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- (54) Title: NOVEL BIOMARKERS OF TYROSINE KINASE INHIBITOR EXPOSURE AND ACTIVITY IN MAMMALS
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[Continued on next page]

Pt #	SU6668 Dose (mg/m ²)	cancer type	gender	Percent Change in Plasma Proteins 12 hr post 2 nd dose /pre-dose							
				SU6668 Cmax (ug/mL)		Tmax hrs	Exposure >2.3 ug/mL (hrs)	AUC ug*hr/mL	PAI-1	VEGF	MMP-9
28	400	prostate	M	13.0	15.0	21.3	164.3	297	46	-27	-21
32	300	ovarian	F	12.9	2.0	11.8	85.7	19	94	-45	-3
34	300	laryngeal	M	11.6	3.5	10.7	136.4	63	-1	156	-2
17	200	colon	F	11.5	2.0	11.0	66.1	221		105	24
25	300	colon	M	11.0	2.0	13.4	75.5	7	-27	184	69
27	400	colon	M	10.3	6.0	9.1	71.2	40	10	-15	-5
19	200	leiomyosarcoma	F	9.5	4.0	12.8	80.2	104	95	36	-0.2
23	300	renal	F	9.3	2.0	8.0	53.5	69	-36	79	-9
16	200	thyroid	F	9.3	2.0	7.3	55.7	263		409	43
24	300	leiomyosarcoma	F	8.2	4.0	16.4	71.2	62	9	18	-27
30	300	testicular	M	7.9	1.0	2.1	32.9	52	82	-66	15
33	300	testicular	M	7.5	5.0	10.4	43.2	20	121	305	99
31	300	hepatocellular	F	6.9	4.0	7.3	55.8	29	100	1	-0
20	200	prostate	M	5.9	2.5	10.9	68.5	47	181	48	-40
26	300	prostate	M	5.6	2.0	8.2	57.0	2	50	38	-21
15	200	breast	F	5.3	2.0	4.8	44.0	95	11	-1	14
35	300	thyroid	M	4.3	1.5	16.1	97.5	65	24	-19	64
22	300	colon	M	2.5	4.0	0.5	20.8	14	23	29	-5
Median											
>500%											
29 to 500 %											
-66 to 28%											

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(57) Abstract: The present invention describes novel methods that measure in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one biomarker in a mammal exposed to a test compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The invention also relates to novel methods, wherein a change in the level of at least one biomarker in a mammal exposed to a compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound, indicates whether the mammal is being exposed to, or is experiencing or will experience a therapeutic or toxic effect in response to, a compound that inhibit tyrosine kinase activity.



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[0001] This application claims benefit of priority from U.S. provisional application Ser. Nos 60/380,872, filed May 17, 2002, 60/448,922, filed February 24, 2003, and 60/448,874, filed February 24, 2003, all of which are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] A biomarker is a molecular marker of a biological event or phenomenon in a organism. Changes in the level of certain biomarkers indicate a biological response to a chemical compound in an organism. Biological responses include events at the molecular, cellular or whole organism level. Changes in biomarker levels can be measured and used to indicate whether or not a particular effect has been achieved in the organism. Changes in biomarker levels can indicate that an organism has been exposed to a particular compound. Changes in biomarker levels also can indicate whether an organism is experiencing or will experience a therapeutic effect or even a toxic event in response to a compound.

SUMMARY OF INVENTION

[0003] The present invention relates to novel methods comprising measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. In the novel methods, the level of at least one biomarker in a mammal exposed to a compound is compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound.

[0004] The invention includes methods for determining whether a test compound inhibits the activity of a protein tyrosine kinase. The invention further relates to methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also discloses methods for determining if a mammal is responsive to the administration of a compound that inhibits tyrosine kinase activity. In addition, the invention relates to methods for identifying mammals that will respond therapeutically to a compound that inhibits VEGFR and/or PDGFR tyrosine kinases. The invention further discloses methods for testing or predicting, as well as kits for determining, whether a mammal will respond therapeutically to a compound that inhibits tyrosine kinase activity. The invention also relates to methods for testing or predicting whether a mammal

will experience an adverse event, such as fatigue, in response to a method of treatment comprising administering a compound that inhibits tyrosine kinase activity.

[0005]

BRIEF DESCRIPTION OF THE FIGURES

[0006] Figure 1 shows the levels of various plasma proteins in plasma from human patients, measured by ELISA, before and 24 hours after the first dose of Compound A (SU6668).

[0007] Figure 2 shows the abundance of a protein (spot #5) in patient plasma, measured by 2D polyacrylamide gel analysis, before and 4 hours after the first dose of Compound A (SU6668).

[0008] Figure 3 shows the identification by mass spectrometry analysis of spot #5 from the 2D gel analysis of patient plasma analyzed in Figure 2.

[0009] Figure 4A shows the change in level of various RNA transcripts, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis. Figure 4B shows the change in the level of vinculin RNA, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis.

[0010] Figure 5 shows the levels of various RNA transcripts, in patient blood samples, on treatment day 28 (27 days after the first dose of Compound A) versus the levels on treatment day 0 (before treatment with Compound A). Numbers shown indicate increase and/or decrease relative to baseline on day 0. No significant change is shown as ~1. Levels decreased are less than 1 and levels increased are greater than 1.

[0011] Figure 6 shows the differential expression of candidate biomarker transcripts in patient PBMC at day 56 relative to day 1 of therapy. The diagram is a depiction of the Affymetrix Difference Calls assigned to each day 56:day 1 expression comparison among the patient sample pairs analyzed via GeneChip hybridization analysis. Letters within blocks represent the Difference Call assigned to each relative expression comparison. The abbreviations are: I = Increase, MI = Marginally Increased, NC = Not Changed; MD = Marginally Decreased; D = Decreased. Cases in which an Increased or Marginally Increased call is assigned to a day 56:day 1 comparison are shaded in gray. Each column represents a different patient. Column headings in each grid represent patient response assessed at the end

of first treatment cycle: PR = partial response, CR = complete response, PD = progressive disease.

[0012] Figures 7A and 7B show the percentage of patients with increased expression of biomarker transcripts following treatment with Compound B (SU5416). Differential expression of six transcripts as measured by microarray and quantitative RT-PCR is presented. The percentage of cases in 5-FU/LV (control) and 5-FU/LV + SU5416 trial arms with increased expression (at predose day 56 relative to predose day 1) of each transcript is displayed. Figure 7A shows the results of the Affymetrix analysis and Figure 7B shows the results from SYBR Green RT-PCR. For the SYBR Green data, an increased is defined as relative expression value of 2-fold or greater. A total of 31 sample pairs were used in RT-PCR analysis; 18 were from SU5416 arm (5 PR, 1 CR, 11 PD and 1 SD response at end of cycle 1), and 13 were from the control arm (9 PR, 3 PD and 1 SD).

[0013] Figure 8 shows the percentage of patients with increased expression of four biomarker transcripts, following treatment with Compound B (SU5416). Differential expression of four transcripts as measured by quantitative RT-PCT is presented. Percentage of cases in CPT-11/5-FU/LV (control) and CPT-11/5-FU/LV + SU5416 trial arms with increased expression (at predose day 42 relative to predose day 1) of four candidate biomarker transcripts in a second SU5416 Phase III clinical trial is displayed. The convention is the same as in panel B in Figure 7. A total of 36 sample pairs was included in this analysis; 18 from the Compound B arm and 18 from the control arm (8 PR and 10 SD responses at end of cycle 1 in each group).

[0014] Figure 9 shows hierarchical clustering of relative expression ratios for four biomarker transcripts. This mosaic depicts association between patient samples and relative expression of the four potential biomarker transcripts. Natural log-transformed SYBR Green RT-PCR ratio data (relative expression of day 56:day 1) were used in analysis. In the color scheme, higher ratios are indicated in red, lower ones in green (scale ranges from -4 to +4). Results from individual patients are oriented as rows and transcripts are oriented as columns. Red bars on the right side of the map indicate cases from the SU4316 arm. The hierarchical clustering method is average linkage and the distance metric is Euclidean.

[0015] Figure 10 shows PAI-1 levels on day 1 and day 56 in patient plasma samples. MR = minor response (cycle 1); PR = partial response (cycle 1); PD = progressive disease (cycle 1)

[0016] Figure 11 shows the mRNA and protein sequences for lactoferrin (SEQ ID NOS 68-69, respectively), lipocalin-2 (SEQ ID NOS 70-71 and 180, respectively), MMP9 (SEQ ID NOS 72 & 66, respectively), and CD24 (SEQ ID NO: 73-74, respectively).

[0017] Figure 12 shows mRNA and protein sequences for eucaryotic initiation factor 4A11 (SEQ ID NOS 75-76, respectively), human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792) (SEQ ID NOS 77-78, respectively), Homo sapiens thymosin beta-10 (SEQ ID NOS 79-80, respectively), Homo sapiens hnRNPcore protein A1 (SEQ ID NOS 81-82, respectively), human leucocyte antigen (CD37) (SEQ ID NOS 83-84, respectively), human MHC call II HLA-DR beta-1 (SEQ ID NOS 85-86, respectively), Homo sapiens translation initiation factor eIF3 p66 subunit (SEQ ID NOS 87-88, respectively), Homo sapiens nm23-H2 gene (SEQ ID NOS 89-90, respectively), human acidic ribosomal phosphoprotein P0 (SEQ ID NOS 91-92, respectively), human cyclophilin (SEQ ID NOS 93-94, respectively), Genbank Accession No. AI541256 (cDNA) (SEQ ID NO: 95), human T-cell receptor active beta chain (SEQ ID NOS 96-97, respectively), human MHC class II lymphocyte antigen (HLA-DP) beta chain (SEQ ID NOS 98-99, respectively), human KIAA0195 (SEQ ID NOS 100-101, respectively), Homo sapiens MAP kinase kinase 3 (MKK3) (SEQ ID NOS 102-103, respectively), human beta-tubulin class III isotype (beta-3) (SEQ ID NOS 104-105, respectively), human tropomyosin (SEQ ID NOS 106-107, respectively), 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C (SEQ ID NOS 108-109, respectively), human MLC emb gene for embryonic myosin alkaline light chain (SEQ ID NOS 110-111, respectively), Homo sapiens glyoxalase II (SEQ ID NOS 112-113, respectively), Homo sapiens trans-golgi network glycoprotein 48 (SEQ ID NOS 114-115, respectively), histone H2B (SEQ ID NOS 116-117, respectively), human RLIP76 protein (SEQ ID NOS 118-119, respectively), Genbank Accession No. W26677 (human retina cDNA) (SEQ ID NO: 120), human PMI gene for a putative receptor protein (SEQ ID NOS 121-122, respectively), human DNA-binding protein A (dbpA) (SEQ ID NOS 123-124, respectively), human ITIH4 (SEQ ID NOS 125-126, respectively), IL-8 (SEQ ID NOS 182-183, respectively) and C-reactive protein (SEQ ID NOS 184-185, respectively).

[0018] Figure 13 shows the changes in VEGF plasma levels, as measured by ELISA, in patients receiving a malate salt of Compound 1 in Trial C.

[0019] Figure 14 shows by hybrid ELISA that VEGF/PLGF heterodimers are detected in plasma of cancer patients and are induced in patients after treatment with a malate salt of Compound 1 in Trial C. The hybrid ELISA assay demonstrates that levels of

heterodimers are increased in 3 of 3 patients tested, and follow a pattern of induction similar to that seen for VEGF and PLGF.

[0020] Figure 15 shows that plasma levels of soluble VEGFR2 decrease in patients in Trial D following treatment with a malate salt of Compound 1 in a dose-dependent manner.

[0021] Figure 16 shows that the decrease in sVEGFR2 following treatment with Compound 1 or malate salt thereof correlates with AUC values (end of C1 dosing, all trials). The scatter graph plots sVEGFR2 fold change (end of cycle 1 dosing over baseline) against AUC values from end of cycle 1 dosing. Results from the first 44 patients (representing 4 trials) are included.

[0022] Figure 17 shows that chemokine MIG is induced in patients during treatment with a malate salt of Compound 1. MIG is a biomarker that also correlates with tumor responses as measured by ¹⁸FDG-PET imaging. Results are from Trial C.

[0023] Figure 18 discloses the amino acid sequence of human vascular endothelial growth factor (VEGF) (SEQ ID NO: 127).

[0024] Figure 19 discloses the amino acid sequence of human placenta growth factor (PLGF) (SEQ ID NO: 128).

[0025] Figure 20 discloses the amino acid sequence of human vascular endothelial growth factor receptor 2 (VEGFR2) (SEQ ID NO: 129).

[0026] Figure 21 discloses the amino acid sequence of human Monokine Induced by Interferon-Gamma (MIG) (SEQ ID NO: 55).

[0027] Figure 22 discloses the amino acid sequence of human interferon-inducible cytokine IP-10 (SEQ ID NO: 130).

[0028] Figure 23 discloses the amino acid sequence of human Interferon-inducible T-cell alpha chemoattractant (I-TAC) (SEQ ID NO: 131).

[0029] Figure 24 shows cDNA or mRNA sequences for human vinculin (SEQ ID NOS 132 & 181, respectively), basic transcription factor 3 homologue (SEQ ID NO: 133), human c-jun proto oncogene (SEQ ID NO: 134), human c-fos proto-oncogen (SEQ ID NO: 135), Homo sapien PTP-nonreceptor type 2 (SEQ ID NO: 136), human cdc2-related protein kinase (SEQ ID NO: 137), human cyclin C (SEQ ID NO: 138), human DNA polymerase-gamma (SEQ ID NO: 139), protein kinase C-alpha (SEQ ID NO: 140), lipocortin II/annexin

A2 (SEQ ID NO: 141), histone H2B member R (SEQ ID NO: 142), Homo sapien amphiregulin (SEQ ID NO: 143), human basic transcription factor 3 (SEQ ID NO: 144), Homo sapien phosphoinositide-3-kinase p110 subunit (SEQ ID NO: 145), human gelsolin (SEQ ID NO: 146), Homo sapien Cyclin D2 (SEQ ID NO: 147), ephrin receptor (EphB4) (SEQ ID NO: 148), human Hanukah factor/granzyme A (SEQ ID NO: 149), von Hippel-Lindau (VHL) tumor suppressor (SEQ ID NO: 150), human mRNA for OB-cadherin-1 (SEQ ID NO: 151), human mRNA for OB-cadherin-2 (SEQ ID NO: 152), phosphoinositol 3-phosphate-binding protein-3 (PEPP3) (SEQ ID NO: 153), human phosphoinositol 3-kinase p85 subunit (SEQ ID NO: 154), human mucin 1 (SEQ ID NO: 155), ErbB3/HER3 receptor tyrosine kinase (SEQ ID NO: 156), and Homo sapien gene for hepatitis C-associated microtubule aggregate protein p44 (nine exons) (SEQ ID NOS 157-164, respectively).

[0030] Figure 25 shows that FLT3 ligand (FL) is induced in patients during treatment with Compound 1.

[0031] Figure 26 demonstrates that interleukin-6 (IL-6) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in IL-6 plasma concentration after treatment with Compound 1 correlates with patient fatigue.

[0032] Figure 27 demonstrates that C-reactive protein (CRP) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in CRP plasma concentration after treatment with Compound 1 correlates with patient fatigue.

[0033] Figure 28 shows that a higher baseline value of CRP in patients with GIST correlates with progressive disease, in Trial D.

[0034] Figure 29 shows that protein expression of OB-cadherin 1 (cadherin 11) is up-regulated in Colo205 xenograph tumors after exposure to Compound 1 for 24 or 48 hours.

BRIEF DESCRIPTION OF THE TABLES

[0035] Tables 1-22 appear following the Examples disclosed in this application, and specifically after Section K.

[0036] Table 1 shows Compound B (SU5416) PBMC sample processing history for Trial A.

[0037] Table 2 shows a list of biomarker transcripts as detected in Affymetrix analysis.

[0038] Table 3 shows primer sequences used in RT-PCR validation analysis.

[0039] Table 4 shows a Mann-Whitney U Test comparison of expression fold change data from Compound B and control arms (Trial A). This statistical analysis was performed to assess the significance of differences in expression change ratios (day 56 vs day 1) between the Compound B and control arms. Separate comparisons were performed of expression change values from Affymetrix analysis and from SYBR Green RT-PCR validation experiments. P-values ≤ 0.05 were considered statistically significant.

[0040] Table 5 shows the Mann-Whitney U Test of Compound B expression data in Trial B.

[0041] Table 6 shows a summary of class prediction results for pooled data (3 gene predictor set).

[0042] Table 7 shows changes in plasma levels of PLGF in patients in Trial C receiving daily treatment with a malate salt of Compound 1.

[0043] Table 8 shows changes in plasma levels of MIG, IP-10, and I-TAC in patients receiving treatment with Compound 1 or a malate salt thereof. Levels of IP-10 and I-TAC at end cycle 1 dosing are estimated values in some cases (>500), as the amount of IP-10 or I-TAC in these samples was higher than the highest standard provided for standard curve generation. All patients represented in this table are from Trial C, except for patient 11 from Trial B and patient 9 from Trial A. Patients in Trial C received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0044] Table 9 shows changes in PLGF and/or sVEGFR2 plasma levels in cancer patients after receiving treatment with Compound 1 or a malate salt thereof. For PLGF, italics text indicates a fold-change of 3-fold or greater, end of cycle 1 dosing relative to day 1. For sVEGFR2, italics text indicates a decrease of 30% or more, end of cycle 1 dosing relative to day 1. Patients in Trials C and D received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0045] Table 10 shows an increase in MIG plasma levels in cancer patients after receiving treatment with Compound 1 or malate salt thereof. As with Table 2, results are from Trial C except for patient 11 from Trial B and patient 9 from Trial A..

[0046] Table 11A shows the change in levels of various mRNA transcripts isolated from Colo205 xenograft tumors, as measured by DNA Array analysis, before exposure to Compound 1, and 6 hours and 24 hours after exposure to the first dose of Compound 1.

[0047] Table 11B shows the change in levels of various mRNA transcripts isolated from SF767 xenograft tumors, measured by DNA Array analysis, before exposure to Compound 1, and 4 hours and 24 hours after exposure to the first dose of Compound 1.

[0048] Table 12 shows the change in the levels of protein expression and/or mRNA transcript abundance in Colo205 xenograft tumors, as measured by Taqman Real Time PCR, before exposure to Compound 1, and at 6 hours versus 24 hours after exposure to the first dose of Compound 1. The following transcripts were measured: Amphiregulin, Cdc2-related protein kinase, phosphoinositol 3-kinase, p110 subunit, cyclin C, OB-Cadherin1, OB-Cadherin2, p85 subunit, Mucin 1, von Hippel-Lindau (VHL) tumor suppressor, ephrin recetor (EphB4), and Gelsolin.

[0049] Table 13 shows the forward and reverse primer and probe sequences used in the TaqMan Real Time PCR Analysis of Colo205 xenograft tumor samples.

[0050] Table 14 lists three sets of 2D gels used in MALDI-TOF-MS and MALDI-MS/MS analysis.

[0051] Table 15 shows the quantification of Spot #1202 from 2D gel analysis. 2D gel analysis was performed on samples isolated from HUVECs that were stimulated with VEGF after pre-treatment with Compound 1 or vehicle control (DMSO).

[0052] Table 16 shows definitive identification of Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-TOF-MS analysis.

[0053] Table 17 identifies Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-MS/MS analysis.

[0054] Table 18 shows quantitative ELISA analysis of pro-MMP1 levels in HUVEC conditioned media, after stimulatation of HUVEC cells with VEGF after pre-treatment with Compound 1 at 10 nM, 100 nM or 1 μ M concentrations, or vehicle control (DMSO).

[0055] Table 19 shows an increase pro-MMP1 levels in patient plasma after treatment with Compound 1. Results are from Study B.

[0056] Table 20 lists the analytes measured using Array 1.1 and Array 2.1 in an antibody chip microassay analysis.

[0057] Table 21 lists 23 biomarkers that show changes in plasma levels following treatment with Compound 1. An up arrow, down arrow or (-) denote relative increase, decrease or no change in detected level respectively, in samples for patients 1, 2 and 3. The

accession numbers for markers, not previously described herein, are as follows: ENA-78 (epithelial derived neutrophil activating protein 78) (SEQ ID NO: 48), P42830; MPIF-1 (myeloid progenitor inhibitory factor 1) (SEQ ID NO: 49), P55773; GCP-2 (gamma tubulin complex component 2) (SEQ ID NO: 50), Q9BSJ2; Amphiregulin (Amphireg) (SEQ ID NO: 51), AAA51781; IL-1 α (interleukin-1 alpha) (SEQ ID NO: 52), NP 000566 for preprotein; IL-1 β (interleukin-1 beta) (SEQ ID NO: 53), NP000567 for preprotein; IL-2 (interleukin-2) (SEQ ID NO: 54), NP000577 for preprotein; MIG (mitogen inducible gene) (SEQ ID NO: 55), NP 061821; NT4 (neurotrophin 4/neurotrophic factor 5) (SEQ ID NO: 56), NP 006170; IGFBP-1 (insulin-like growth factor binding factor-1) (SEQ ID NO: 57), NP 000587; GRO- β (SEQ ID NO: 58), AAA63183; TNFR1 (tumor necrosis factor receptor 1) (SEQ ID NO: 59), P19438; FLT3 ligand (fms-like tyrosine kinase ligand/Flk 2 ligand) (SEQ ID NO: 60), I38440; IL-6 (interleukin-6) (SEQ ID NO: 61), NP-000591; MCP-1 (monocyte chemoattractant protein 1) (SEQ ID NO: 62), P13500; TNF α (tumor necrosis factor alpha) (SEQ ID NO: 63), NP 000585; TARC (thymus and activation regulated chemokine) (SEQ ID NO: 64), Q92583; MMP7 (SEQ ID NO: 65), NP 002414 for preprotein; MMP9 (SEQ ID NO: 66), NP 004985 for preprotein; and leptin (SEQ ID NO: 67), NP000221 for preprotein. Note that accession numbers and SEQ ID NOs in this specification are used to identify cDNAs, mRNAs or proteins of interest, rather limit the biomarkers to specific sequences.

[0058] Table 22 shows the relative fold change of six plasma biomarkers in three patients (denoted 1, 2 and 3) following Compound 1 treatment relative to predose, as measured by two methods: ELISA; and antibody chip technology (MSI).

DETAILED DESCRIPTION OF THE INVENTION

[0059] The present invention relates to novel methods for determining whether a test compound inhibits tyrosine kinase activity and novel methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also relates to novel methods for determining whether a mammal is experiencing or will experience a particular biological phenomenon, such as a therapeutic effect, “responding” (as defined herein), or an adverse event, in response to a compound that inhibit tyrosine kinase activity.

[0060] The novel methods comprise measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one

biomarker in the mammal exposed with a test compound, as compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The tyrosine kinases of the novel methods include, but are not limited to, those selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor.

[0061] In certain embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone, as described herein, and also in U.S. Serial No. 10/281,266. In other embodiments, the tyrosine kinase inhibitor comprises compounds described in U.S. Ser. No. 09/783,264, WO 01/60814, U.S. Ser. No. 10/076,140, U.S. Ser. No. 10/281,266, U.S. Ser. No. 10/281,985, U.S. Ser. No. 10/237,966 (now a U.S. provisional application), as well as a U.S. provisional application Ser. No. 60/448,861, filed February 24, 2003 (entitled "Treatment of excessive osteolysis with indolinone compounds"), all of which are hereby incorporated by reference.

[0062] Identification of biomarkers that provide rapid and accessible readouts of efficacy, drug exposure, or clinical response is increasingly important in the clinical development of drug candidates. Embodiments of the invention include measuring changes in the expression levels of secreted proteins, or plasma markers, which represent one category of biomarker. In one embodiment, plasma samples, which represent a readily accessible source of material, serve as a surrogate tissue for biomarker analysis.

A. Definitions

[0063] Unless otherwise stated the following terms used in the specification and claims have the meanings discussed below.

[0064] "Test compound" refers to any pharmaceutical composition that inhibits or modulates a protein tyrosine kinase.

[0065] "Tyrosine kinase modulator" or "tyrosine kinase inhibitor" refers to any chemical composition that modulates, affects, alters, inhibits or reduces the enzymatic activity or tyrosine phosphorylation action of a tyrosine kinase.

B. Biomarkers Modulated in Mammals Exposed to Tyrosine Kinase Inhibitors

[0066] In one embodiment, the invention includes a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPs core protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

[0067] Alternatively, a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

[0068] In an other embodiment, the invention includes a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFa, TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated

microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

[0069] Alternatively, a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative

receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

[0070] In an other embodiment, the invention includes a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens

trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

[0071] Alternatively, a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPs core protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase)

precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

[0072] In another embodiment, the invention includes a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1,

GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal is responding to the compound that inhibits tyrosine kinase activity.

[0073] Alternatively, a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the compound; and

(b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPs core protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic

transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

[0074] The term “responding” encompasses responding by way of a biological and cellular response, as well as a clinical response (such as improved symptoms, a therapeutic effect or an adverse event), in a mammal.

[0075] In another embodiment, the invention includes a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation

initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

[0076] In another embodiment, the invention includes a method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFa, TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in a same type of mammal without cancer the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the

mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

[0077] As used throughout the specification, the term “respond therapeutically” refers to the alleviation or abrogation of a disease, such as cancer. This term means that the life expectancy of an individual affected with the disease will be increased or that one or more of the symptoms of the disease will be reduced or ameliorated. The term encompasses a reduction in cancerous cell growth or tumor volume. Whether a mammal responds therapeutically can be measured by many methods well known known in the art, such as PET imaging.

[0078] In another embodiment, the mammal is a human. In other embodiments, the mammal is a rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate, or monkey.

[0079] In other embodiments, any of the proceeding methods is an in vitro method, and the protein and/or mRNA biomarker is measured in at least one mammalian biological tissue. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological fluid, including but not limited to whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological tissue including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

[0080] In yet other embodiments, the methods of the invention are carried out on mammals who have cancer. The cancer can be, for example, but is not limited to, prostate cancer, colorectal cancer (CRC), thyroid cancer, an advanced solid malignancy, pancreatic cancer, breast cancer, parotid cancer, synovial cell cancer or sarcoma, gastrointestinal stromal tumor (GIST), laryngeal cancer, testicular cancer, leiomyosarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, ovary cancer, lung cancer, colon cancer, renal cell carcinoma, sarcoma, retroperitoneal sarcoma, pelvic sarcoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, neuroendocrine cancer, bronchial adenocarcinoma, head and neck cancer and/or thymic cancer.

[0081] In other embodiments, any of the preceding methods also comprise a step wherein the mammal is also exposed to a cancer chemotherapeutic agent before, during and/or after exposure to the compound that inhibits tyrosine kinase activity.

[0082] Other embodiments also include any of the proceeding methods, wherein the “difference” refers to an increase in the level of at least one of the following protein(s) and/or

mRNA transcript(s): PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGR/PLGR heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2B, human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFa, TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ephrin receptor EphB4, OB-cadherin 1, phosphoinositol 3-kinase p85 subunit, mucin 1 and gelsolin, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0083] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of prostate cancer, colon cancer, thyroid cancer and an advance solid malignancy, and wherein the “difference” refers to an increase in the level of VEGF protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of VEGF protein and/or mRNA transcript as measured before exposure to the compound.

[0084] Other embodiments also include any of the proceeding methods wherein the mammal has colon or colorectal cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, MMP-9, lactoferrin, lipocalin-2, and/or CD24 antigen protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0085] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of synovial sarcoma, rectal cancer, gall-bladder cancer,

hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, colon cancer, renal cell carcinoma, sarcoma, retroperitoneal sarcoma, pelvis sarcoma, parotid cancer, uterine cancer, pelvic angiosarcoma, colorectal cancer and gastrointestinal stromal tumor (GIST), and wherein the “difference” refers to an increase in the level of at least one of VEGF, PLGF and VEGF/PLGF heterodimers protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0086] Other embodiments also include any of the proceeding methods wherein the mammal has an advanced solid malignancy, and wherein the “difference” refers to an increase in the level of VEGF and/or MMP-9 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0087] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of pancreatic cancer, synovial sarcoma, colon cancer, non-small cell lung cancer (NSCLC), rectal cancer, pelvis sarcoma, and sarcoma and/or bronchial adenocarcinoma, and wherein the “difference” refers to an increase in the level of at least one of MIG, IP-10 and I-TAC protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0088] Other embodiments also include any of the proceeding methods wherein the mammal has thyroid cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2b and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0089] Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the “difference” refers to an increase in the level of at least one of eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0090] Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the “difference” refers to an increase in the level of at least one of human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0091] Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0092] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the “difference” refers to an increase in the level of at least one of Homo sapiens thymosin beta-10 gene, Homo sapiens MAP kinase kinase 3

(MKK3) and histone H2B member R protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0093] Other embodiments also include any of the proceeding methods wherein the mammal has synovial cell cancer, and wherein the “difference” refers to an increase in the level of human RLIP76 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of human RLIP76 protein and/or mRNA transcript as measured before exposure to the compound.

[0094] Other embodiments also include any of the proceeding methods, wherein the “difference” refers to a decrease in the level of at least one of the following protein(s) and/or mRNA transcript(s): ITIH4, PAI-1, soluble VEGF receptor 2 (sVEGFR2), Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78, MPIF-1, MMP7, MIG, cdc2 related protein kinase, and phosphoinositol 3-kinase p110 subunit, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0095] Other embodiments also include any of the proceeding methods wherein the mammal has is at least one of breast cancer, prostate cancer and thyroid cancer, and wherein the “difference” refers to a decrease in the level of ITIH4 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of ITIH4 protein and/or mRNA transcript as measured before exposure to the compound.

[0096] Other embodiments also include any of the proceeding methods wherein the mammal has at least one of synovial sarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, melanoma, colon cancer, renal cell carcinoma, non-small cell lung cancer (NSCLC), sarcoma, retroperitoneal sarcoma, pelvis sarcoma, squamous cell carcinoma parotid cancer, bronchial adenocarcinoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, colorectal cancer (CRC), neuroendocrine cancer, gastrointestinal stromal tumor (GIST), head and neck cancer, thymic cancer and thyroid cancer, and wherein the “difference” refers to a decrease in the level of sVEGFR2 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of sVEGFR2 protein and/or mRNA transcript as measured before exposure to the compound.

[0097] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the “difference” refers to a decrease in the level of at least one of Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human beta-tubulin class III isotype (beta-3), and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0098] Other embodiments also include any of the proceeding methods wherein the mammal has thyroid cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0099] Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo

sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0100] Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the “difference” refers to a decrease in the level of at least one of human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0101] Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, Homo sapiens trans-golgi network glycoprotein 48, histone H2B and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

[0102] In another embodiment, the invention also includes a kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic

ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

[0103] In another embodiment, the invention also includes the preceding kit, wherein the instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens

cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and
(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

[0104] wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

[0105] In another embodiment, the invention also includes a method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

- (b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;
- (c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

[0106] As used in the specification, the term “adverse event” refers to a physiological effect in a mammal, such as fatigue or other side effect, that is severe enough to warrant altering, reducing or eliminating the mammal’s exposure to a particular tyrosine kinase inhibitor. Exposure or administration can be altered, reduced or eliminated in terms of the amount or dosage of the tyrosine kinase inhibitor, as well as length of time and/or frequency of exposure. A determination as to whether a particular physiological effect is severe enough to be considered “an adverse event” falls within the judgment of those skilled in the art, such as a laboratory scientist, veterinarian or medical practitioner.

C. Further Embodiments of the Novel Methods

1. Measurement of Protein and mRNA

[0107] In other embodiments, the novel methods of Section B are carried out so that the step where the mammal is exposed to test compound includes administration of at least one dose of test compound, or at least two doses, or at least 5 doses or at least 10 doses, up to at least 55 or 56 doses. In certain embodiments, these doses are administered during a period of 4 hours, 6 hours, or 24 hours to about 100 days. In further embodiments, the doses are administered over a period of 24 hours, 2 days, or 28 days. In other embodiments, two doses are administered per every 24 hours, and in other embodiments, the doses are administered about every 12 hours. It will be understood by those of skill in the art that the administration of test compound, according to the exposure steps of the methods of Section B, can be varied to suit individual needs of the mammal being treated, the compound being administered, the method of administration and the disease being treated. For example, in a typical dosing regimen, the patient receives one dose per day of test compound, for a number of days, such

as about 28 or about 56 days. In other dosing regimens, the test compound is administered about once per day, twice per week, or once per week.

[0108] The measurement of protein and/or RNA, following the exposure step in the methods of Section B, can be carried out on a sample from the mammal taken about 4 or 6 hours following the first dose (exposure) of the mammal to test compound. In other embodiments, this measurement is carried out on a sample taken 12 hours, 1 day, 2 days, up to about 100 days, after the first dose (exposure) of the mammal to test compound. In other embodiments, the protein and/or mRNA measurements are taken from samples from the mammals 4 or 6 hours after the first dose of test compound or 24 hours after the first dose of test compound, or 15 or 28 days after the first dose of test compound. Typically, dosing of test compound will be periodic between the first and last dose of test compound that precedes the sample taken for measurement of biomarker protein and/or mRNA. For example, the test compound is administered once a day, every day for 28 days. Typically, the mammal sample taken (for measurement of biomarker protein and/or mRNA) will be taken shortly following the most recent dose of test compound, for example within 24 of the most recent dose of test compound.

[0109] In other embodiments, the methods of Section B are carried out so that the measurement of protein and/or mRNA is carried out on a mammalian tissue selected from biological fluids, including but not limited to the group of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, saliva, and other tissues including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue, bone marrow.

[0110] In other embodiments, the methods of Section B are carried out on a mammal that is further exposed to other chemotherapeutic agents, including but not limited to 5-fluoro-uracil (5-FU), leucovorin, CPT11, aromasin, taxol, paclitaxel, other "standard of care" agents used in patients, COX-2 inhibitors (such as celecoxib), and other tyrosine kinase inhibitors. Such exposure to a cancer chemotherapeutic agent can be before, during and/or after exposure to test compound.

[0111] In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least

25%. In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 2-, 3-, 5-, 10-, 15- or 24-fold. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5-, 3.0-, 3.5-, 4.0-, 4.2-, 4.5-, 5.0-, 5.5-, 6.0-, 6.1-, 6.5-, 7.0-, 7.3-, 10.0-, 15.0-, 19.0- or 24-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 1.7- or 2.0-fold.

[0112] In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 25%. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5-, 3.0-, 3.5- or 3.7-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 1.7- or 2.0-fold.

[0113] To quantify the protein and/or mRNA measured in the novel methods of Section B, methods well known to the skilled artisan are used. For example, quantification of protein can be carried out using methods such as ELISA, 2-dimensional SDS PAGE, Western Blot, immunoprecipitation, immunohistochemistry, fluorescense activated cell sorting (FACS), flow cytometry. Quantification of mRNA is measured using methods such as PCR, array hybridization, Northern blot, in-situ hybridization, dot-blot, Taqman, RNase protection assay.

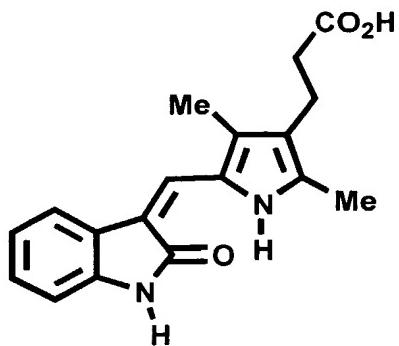
[0114] In further embodiments of the invention, the methods of Section B are carried out so that the level of at least two, or at least three, or at least four, or at least five, or at least 6, or at least seven or at least eight, or at least nine, up to 87 of the biomarkers are measured in a mammal. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 66 biomarkers of Section B that are increased upon exposure of a mammal to a compound that inhibits tyrosine kinase. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 39 biomarkers of Section B that are decreased upon exposure of a mammal to a compound that inhibits tyrosine kinase.

2. Tyrosine Kinase and Inhibitors of Tyrosine Kinase

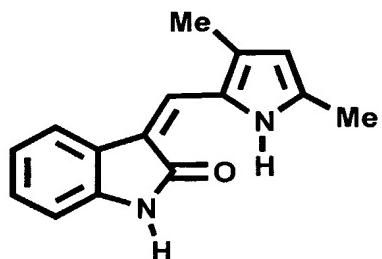
[0115] In certain embodiments, the tyrosine kinases of the novel methods are selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor. See, for example, U.S. Pat. No. 6,177,401 (Flk-1), WO 01/45689 (c-kit), GenBank Accession No. NM 002609 (PDGFR-beta), GenBank Accession No. NM 006206 (PDGFR-alpha), GenBank Accession No. NM 023109 (FGFR-1), GenBank Accession No. NM 023028 (FGFR-2) and GenBank Accession No. NP_005202 (c-fms/CSF-1 receptor).

[0116] FLT3 (fms like tyrosine kinase 3) is a member of the class III receptor tyrosine kinases. Those of skill in the art will recognize that FLT3 has also been called “flk2” in the scientific literature. “FLT3” as used herein, refers to a polypeptide having, for example, the sequence set forth in accession number gi|4758396|ref|NP_004110.1| fms-related tyrosine kinase 3 [Homo sapiens], or gi|544320|sp|P36888|FLT3_HUMAN FL CYTOKINE RECEPTOR PRECURSOR (TYROSINE-PROTEIN KINASE RECEPTOR FLT3) (STEM CELL TYROSINE KINASE 1) (STK-1) (CD135 ANTIGEN), or gi|409573|gb|AAA18947.1| (U02687) serine/threonine protein kinase [Homo sapiens]. Corresponding mRNA accessions for the first two sequences are gi|4758395|ref|NM_004119.1| Homo sapiens fms-related tyrosine kinase 3 (FLT3), mRNA gi|406322|emb|Z26652.1|HSFLT3RTK H.sapiens FLT3 mRNA for FLT3 receptor tyrosine kinase.

[0117] In other embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone compound. In another embodiment, the test compound is a compound of Formula I. These, and other exemplary tyrosine kinase inhibitors, are shown below. The skilled artisan will recognize that the novel methods of the invention can be used to test any tyrosine kinase inhibitor, in addition to those listed below.



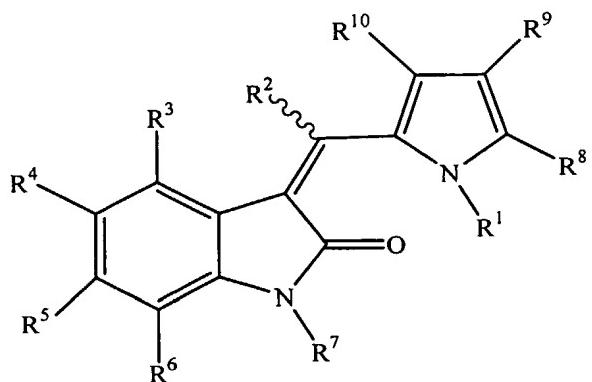
[0118] Compound A (SU6668): 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid.



[0119] Compound B (SU5416): 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one.

[0120]

A pyrrole substituted 2-indolinone having the formula:



wherein:

R¹, R² and R⁷ are hydrogen;

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

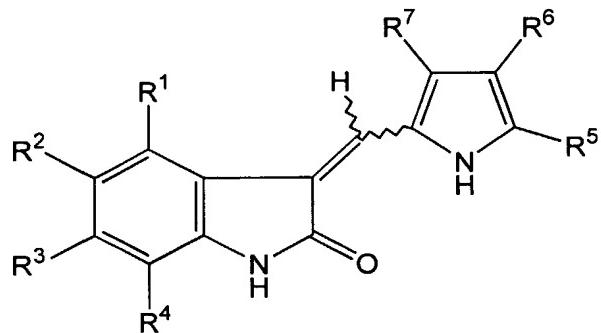
R⁸ is unsubstituted lower alkyl;

R⁹ is -(CH₂)(CH₂)C(=O)OH; and

R¹⁰ is unsubstituted lower alkyl.

[0121]

A compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclic, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, $-(CH_2)_tR^{16}$ and $-C(O)NR^8R^9$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-C(O)R^{15}$, aryl, heteroaryl, and $-S(O)_2NR^{13}R^{14}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, aryl, heteroaryl, $-NR^{13}S(O)_2R^{14}$, $-S(O)_2NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-NR^{13}C(O)OR^{14}$ and $-SO_2R^{20}$ (wherein R^{20} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^4 is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and $-NR^{13}R^{14}$;

R^5 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^6 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $-C(O)R^{17}$ and $-C(O)R^{10}$; or

R^6 and R^7 may combine to form a group selected from the group consisting of $-(CH_2)_4-$, $-(CH_2)_5-$ and $-(CH_2)_6-$;

with the proviso that at least one of R^5 , R^6 or R^7 must be $-C(O)R^{10}$;

R⁸ and R⁹ are independently selected from the group consisting of hydrogen, alkyl and aryl;

R¹⁰ is selected from the group consisting of hydroxy, alkoxy, aryloxy, -N(R¹¹)(CH₂)_nR¹², and -NR¹³R¹⁴;

R¹¹ is selected from the group consisting of hydrogen and alkyl;

R¹² is selected from the group consisting of -NR¹³R¹⁴, hydroxy, -C(O)R¹⁵, aryl, heteroaryl, -N⁺(O⁻)R¹³R¹⁴, -N(OH)R¹³, and -NHC(O)R^a (wherein R^a is unsubstituted alkyl, haloalkyl, or aralkyl);

R¹³ and R¹⁴ are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R¹³ and R¹⁴ may combine to form a heterocyclo group;

R¹⁵ is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

R¹⁶ is selected from the group consisting of hydroxy,

-C(O)R¹⁵, -NR¹³R¹⁴ and -C(O)NR¹³R¹⁴;

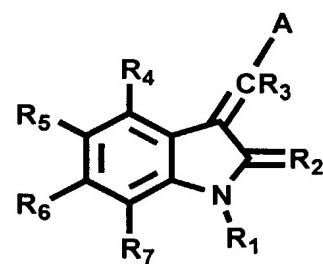
R¹⁷ is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

R²⁰ is alkyl, aryl, aralkyl or heteroaryl; and

n and r are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

[0122] A compound having the formula:



wherein:

R₁ is H;

R₂ is O or S;

R₃ is hydrogen;

R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, and CONRR';

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkyfurran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R or CONRR';

n is 0-3;

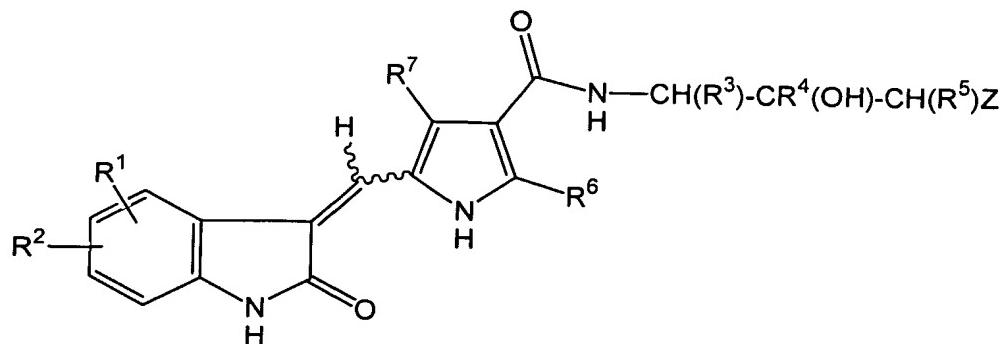
R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof.

[0123]

A compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy, $-C(O)R^8$, $-NR^9R^{10}$ and $-C(O)NR^{12}R^{13}$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-C(O)R^8$, $-S(O)_2NR^9R^{10}$ and $-SO_2R^{14}$ (wherein R^{14} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^3 , R^4 and R^5 are independently hydrogen or alkyl;

Z is aryl, heteroaryl, heterocycle, or $-NR^{15}R^{16}$ wherein R^{15} and R^{16} are independently hydrogen or alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are attached from a heterocycloamino group;

R^6 is selected from the group consisting of hydrogen or alkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and $-C(O)R^{17}$ as defined below;

R^8 is selected from the group consisting of hydroxy, alkoxy and aryloxy;

R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

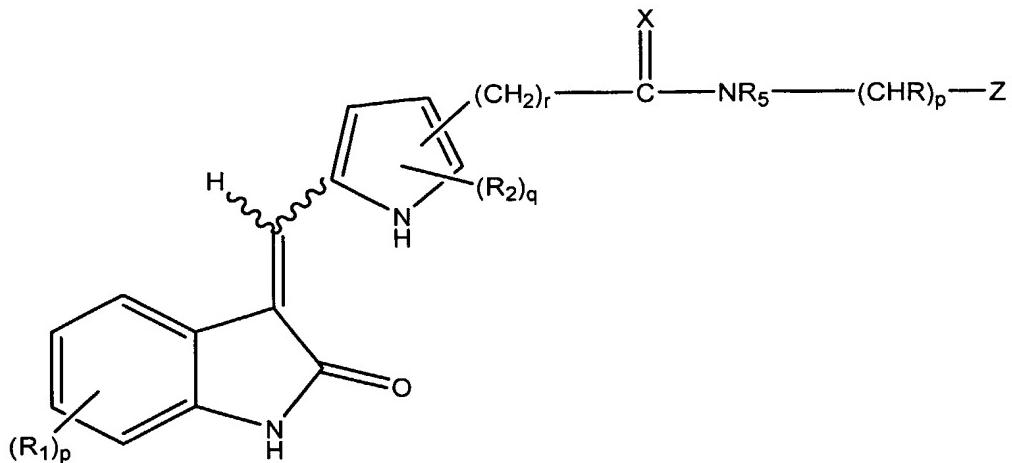
R^9 and R^{10} combine to form a heterocycloamino group;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a heterocycloamino;

R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

[0124] In other embodiments of the invention, a mammal is exposed to a compound of Formula I:



(I),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R₁ is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈, -NR₉R₁₀, -NR₉C(O)-R₁₂ and -C(O)NR₉R₁₀;

each R₂ is independently selected from the group consisting of alkyl, aryl, heteroaryl, -C(O)-R₈, and SO₂R'', where R'' is alkyl, aryl, heteroaryl, NR₉N₁₀ or alkoxy;

each R₅ is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈ and (CHR)_rR₁₁;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

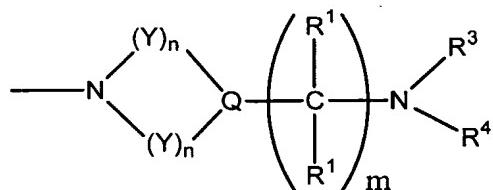
R₈ is selected from the group consisting of -OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R₉ and R₁₀ are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R₉ and R₁₀ together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R₁₁ is selected from the group consisting of -OH, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R₁₂ is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or -NR₃R₄, where R₃ and R₄ are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R₃ and R₄ may combine with N to form a ring where the ring atoms are selected from the group consisting of CH₂, N, O and S or



wherein Y is independently CH₂, O, N or S,

Q is C or N;

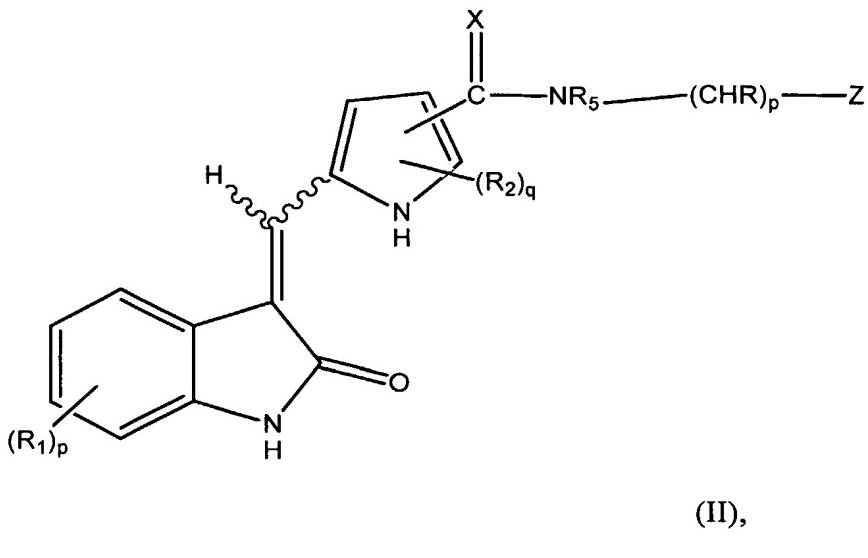
n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

[0125]

In another embodiment, a mammal is exposed to a compound of Formula II:



wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R₁ is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈, -NR₉R₁₀, -NR₉C(O)-R₁₂ and -C(O)NR₉R₁₀;

each R₂ is independently selected from the group consisting of alkyl, aryl, heteroaryl, -C(O)-R₈, and SO₂R'', where R'' is alkyl, aryl, heteroaryl, NR₉N₁₀ or alkoxy;

each R₅ is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈ and (CHR)_rR₁₁;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

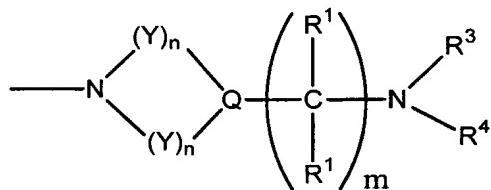
R₈ is selected from the group consisting of -OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R₉ and R₁₀ are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R₉ and R₁₀ together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of $-OH$, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH , O -alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2 , N, O and S or



wherein Y is independently CH_2 , O, N or S,

Q is C or N;

n is independently 0-4; and

m is 0-3;

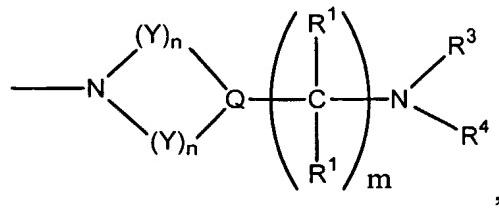
or a pharmaceutically acceptable salt thereof.

[0126] In another embodiment of the invention, a mammal is exposed to a compound of Formula I or II, wherein R_1 is halo (e.g., F and Cl) and Z is $-NR_3R_4$ wherein R_3 and R_4 are independently H or alkyl.

[0127] In another embodiment, Z of Formula I or II is $-NR_3R_4$, wherein R_3 and R_4 form a morpholine ring.

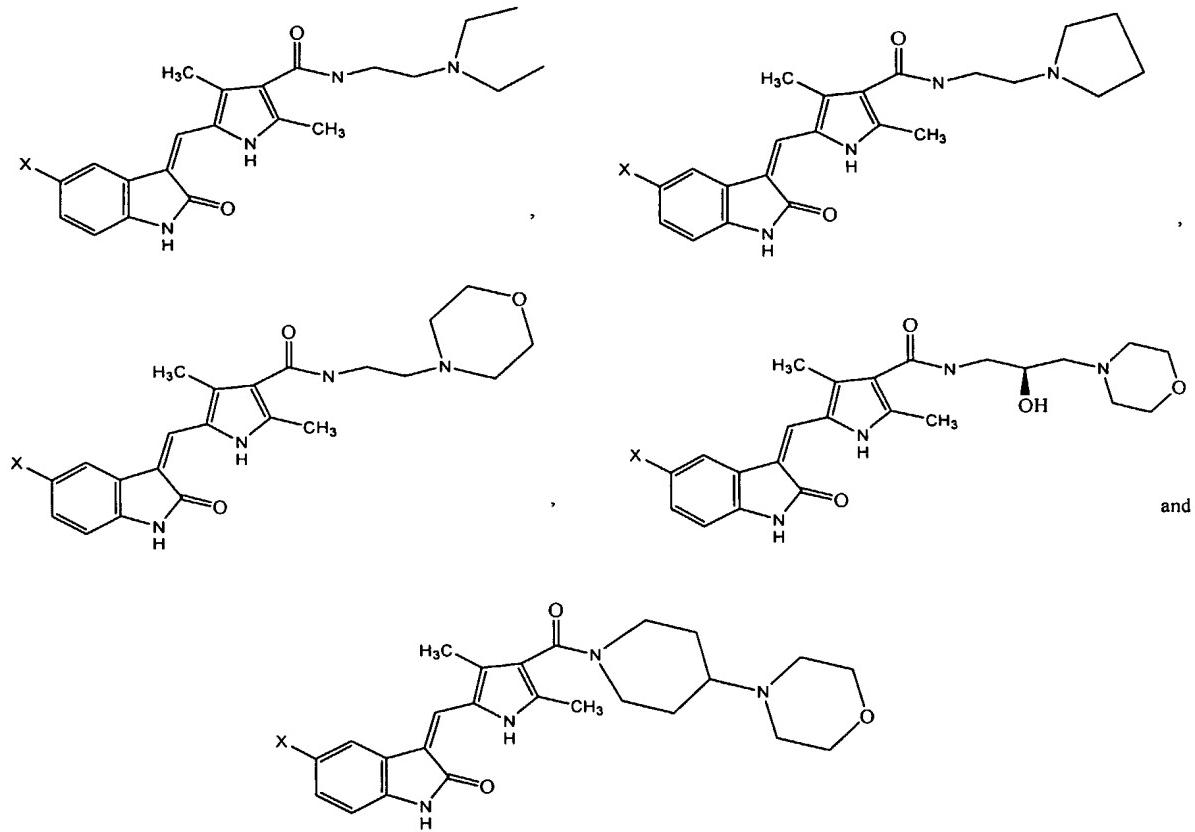
[0128]

In another embodiment, Z of Formula I or II is:



wherein each Y is CH₂, each n is 2, m is 0 and R₃ and R₄ form a morpholine ring.

[0129] In another embodiment of the invention, a mammal is exposed to a compound selected from the group consisting of



wherein X is F, Cl, I or Br; or a pharmaceutically acceptable salt thereof. In another embodiment, X is F.

[0130] In another embodiment of the invention, a mammal is exposed to a compound of Formula I selected from the group consisting of:

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (Compound 2);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (Compound 3);

(S)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 4);

(R)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 5);

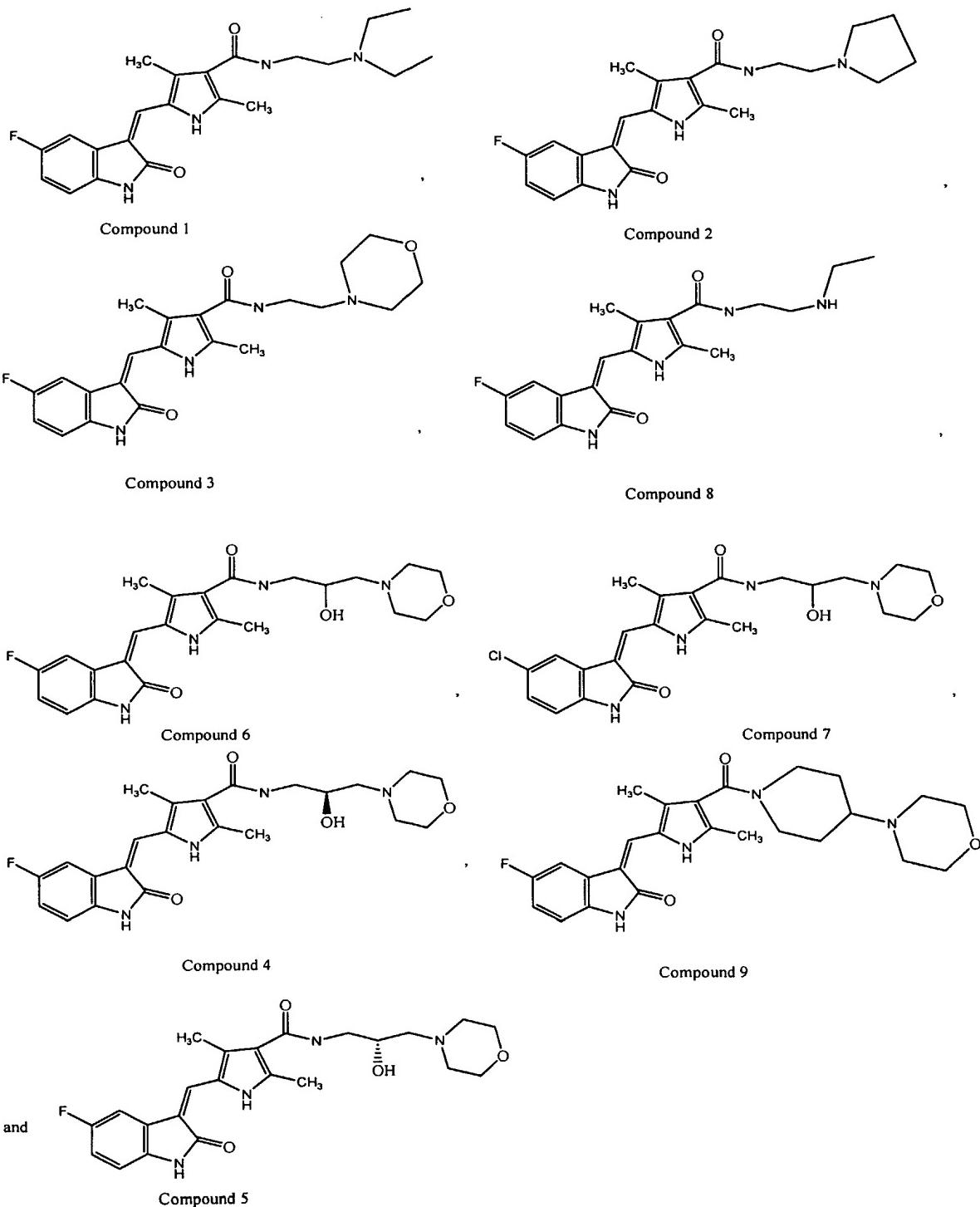
5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 6);

5-(5-Chloro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 7);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-ethylamino-ethyl)-amide (Compound 8);

3-[3,5-dimethyl-4-(4-morpholin-4-yl-piperidine-1-carbonyl)-1H-pyrrol-2-methylene]-5-fluoro-1,3-dihydro-indol-2-one (Compound 9).

[0131] The above compounds are shown below:



[0132] To clearly set forth the compounds of Formula I, Formula II and other compounds of the formulas described herein, useful in the inventive method, the following definitions are provided.

[0133] "Alkyl" refers to a saturated aliphatic hydrocarbon radical including straight chain and branched chain groups of 1 to 20 carbon atoms (whenever a numerical range; e.g. "1-20", is stated herein, it means that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms).

Alkyl groups containing from 1 to 4 carbon atoms are referred to as lower alkyl groups.

When said lower alkyl groups lack substituents, they are referred to as unsubstituted lower alkyl groups. More preferably, an alkyl group is a medium size alkyl having 1 to 10 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and the like. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, or tert-butyl, and the like. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more preferably one to three, even more preferably one or two substituent(s) independently selected from the group consisting of halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto, (unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR,

RC(O)O-, and $-NR_{13}R_{14}$, wherein R₁₃ and R₁₄ are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, cycloalkyl, heterocyclic and aryl optionally substituted with one or more, groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups.

[0134] Preferably, the alkyl group is substituted with one or two substituents independently selected from the group consisting of hydroxy, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, or $-NR_{13}R_{14}$, wherein R₁₃ and R₁₄ are independently selected from the group consisting of hydrogen and alkyl. Even more preferably the alkyl group is substituted with one or two substituents which are independently of each other hydroxy, dimethylamino, ethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, morpholino, piperazino, 4-lower alkylpiperazino, phenyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolyl, triazinyl, and the like.

[0135] "Cycloalkyl" refers to a 3 to 8 member all-carbon monocyclic ring, an all-carbon 5-member/6-member or 6-member/6-member fused bicyclic ring or a multicyclic fused ring (a "fused" ring system means that each ring in the system shares an adjacent pair of carbon atoms with each other ring in the system) group wherein one or more of the rings may contain one or more double bonds but none of the rings has a completely conjugated pi-electron system.

[0136] Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, adamantane, cycloheptane, cycloheptatriene, and the like. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more

preferably one or two substituents, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen atoms of the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present)atoms in the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto,(unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR, RC(O)O-, and -NR₁₃R₁₄ are as defined above.

[0137] "Alkenyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like.

[0138] "Alkynyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. Representative examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2-, or 3-butynyl, and the like.

[0139] "Aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups of 1 to 12 carbon atoms having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted.

When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto,(unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR, RC(O)O-, and -NR₁₃R₁₄, with R₁₃ and R₁₄ as defined above. Preferably, the aryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0140] "Heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine and carbazole. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two, or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto,(unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR, RC(O)O-, and -NR₁₃R₁₄, with R₁₃ and R₁₄ as defined above. Preferably, the heteroaryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0141] "Heterocyclic" refers to a monocyclic or fused ring group having in the ring(s) of 5 to 9 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heterocyclic groups are pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, homopiperazino, and the like. The heterocyclic ring may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted

lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto,(unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)₂-, -C(O)OR, RC(O)O-, and -NR₁₃R₁₄, with R₁₃ and R₁₄ as defined above. Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0142] Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0143] "Hydroxy" refers to an -OH group.

[0144] "Alkoxy" refers to both an -O-(unsubstituted alkyl) and an -O-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

[0145] "Aryloxy" refers to both an -O-aryl and an -O-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenoxy, pyridinyloxy, furanyloxy, thienyloxy, pyrimidinyloxy, pyrazinyloxy, and the like, and derivatives thereof.

[0146] "Mercapto" refers to an -SH group.

[0147] "Alkylthio" refers to both an -S-(unsubstituted alkyl) and an -S-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methylthio, ethylthio, propylthio, butylthio, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, and the like.

[0148] "Arylthio" refers to both an -S-aryl and an -S-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenylthio, pyridinylthio, furanylthio, thienylthio, pyrimidinylthio, and the like and derivatives thereof.

[0149] "Acyl" refers to a -C(O)-R" group, where R" is selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, unsubstituted cycloalkyl, aryl optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihalomethyl, unsubstituted lower alkoxy, halo and -NR₁₃R₁₄ groups, heteroaryl (bonded through a ring carbon) optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and -NR₁₃R₁₄ groups and heterocyclic (bonded through a ring carbon)

optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and

$-NR_{13}R_{14}$ groups. Representative acyl groups include, but are not limited to, acetyl, trifluoroacetyl, benzoyl, and the like.

[0150] "Aldehyde" refers to an acyl group in which R" is hydrogen.

[0151] "Thioacyl" refers to a $-C(S)-R"$ group, with R" as defined herein.

[0152] "Ester" refers to a $-C(O)O-R"$ group with R" as defined herein except that R" cannot be hydrogen.

[0153] "Acetyl" group refers to a $-C(O)CH_3$ group.

[0154] "Halo" group refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

[0155] "Trihalomethyl" group refers to a $-CX_3$ group wherein X is a halo group as defined herein.

[0156] "Methylenedioxy" refers to a $-OCH_2O-$ group where the two oxygen atoms are bonded to adjacent carbon atoms.

[0157] "Ethylenedioxy" group refers to a $-OCH_2CH_2O-$ where the two oxygen atoms are bonded to adjacent carbon atoms.

[0158] "S-sulfonamido" refers to a $-S(O)_2NR_{13}R_{14}$ group, with R₁₃ and R₁₄ as defined herein.

[0159] "N-sulfonamido" refers to a $-NR_{13}S(O)_2R$ group, with R₁₃ and R as defined herein.

[0160] "O-carbamyl" group refers to a $-OC(O)NR_{13}R_{14}$ group with R₁₃ and R₁₄ as defined herein.

[0161] "N-carbamyl" refers to an $ROC(O)NR_{14}-$ group, with R and R₁₄ as defined herein.

[0162] "O-thiocarbamyl" refers to a $-OC(S)NR_{13}R_{14}$ group with R₁₃ and R₁₄ as defined herein.

[0163] "N-thiocarbamyl" refers to a $ROC(S)NR_{14}-$ group, with R and R₁₄ as defined herein.

[0164] "Amino" refers to an $-NR_{13}R_{14}$ group, wherein R₁₃ and R₁₄ are both hydrogen.

[0165] "C-amido" refers to a $-C(O)NR_{13}R_{14}$ group with R₁₃ and R₁₄ as defined herein.

[0166] "N-amido" refers to a RC(O)NR_{14} - group, with R and R_{14} as defined herein.

[0167] "Nitro" refers to a $-\text{NO}_2$ group.

[0168] "Haloalkyl" means an unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above that is substituted with one or more same or different halo atoms, e.g., $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CCl}_3$, and the like.

[0169] "Aralkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with an aryl group as defined above, e.g., $-\text{CH}_2\text{phenyl}$, $-(\text{CH}_2)_2\text{phenyl}$, $-(\text{CH}_2)_3\text{phenyl}$, $\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{phenyl}$, and the like and derivatives thereof.

[0170] "Heteroaralkyl" group means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with a heteroaryl group, e.g., $-\text{CH}_2\text{pyridinyl}$, $-(\text{CH}_2)_2\text{pyrimidinyl}$, $-(\text{CH}_2)_3\text{imidazolyl}$, and the like, and derivatives thereof.

[0171] "Monoalkylamino" means a radical $-\text{NHR}'$ where R' is an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., methylamino, (1-methylethyl)amino, cyclohexylamino, and the like.

[0172] "Dialkylamino" means a radical $-\text{NR}'\text{R}''$ where each R' is independently an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., dimethylamino, diethylamino, (1-methylethyl)-ethylamino, cyclohexylmethylamino, cyclopentylmethylamino, and the like.

[0173] "Cyanoalkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above, which is substituted with 1 or 2 cyano groups.

[0174] "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocycle group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycle group is substituted with an alkyl group and situations where the heterocycle group is not substituted with the alkyl group.

[0175] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or physiologically/pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0176] As used herein, a "physiologically/pharmaceutically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

[0177] An "pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[0178] As used herein, the term "salt" of a compound of Formula I, II or other formulas or compounds described in this specification refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts include:

(i) acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably hydrochloric acid or (L)-malic acid such as the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid(2-diethylaminoethyl)amide; or

(ii) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0179] "Method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by, practitioners of the chemical, pharmaceutical, biological, biochemical and medical arts.

[0180] "In vivo" refers to procedures performed within a living organism such as, without limitation, a mouse, rat or rabbit.

[0181] "Treat", "treating" and "treatment" refer to a method of alleviating, ameliorating, abrogating or relieving a disease condition and/or any of its attendant symptoms.

[0182] "Patient" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukariotic cell or as complex as a mammal, including a human being.

[0183] "Therapeutically effective amount" refers to that amount of the compound being administered which will prevent, alleviate, ameliorate or relieve to some extent, one or more of the signs or symptoms of the disorder being treated.

ADMINISTRATION AND PHARMACEUTICAL COMPOSITION

[0184] In another embodiment of the invention, a human patient is exposed or administered a compound of Formula I, Formula II or other formulas or compounds described in this application, or a pharmaceutically acceptable salt thereof. Alternatively, the compounds of Formula I, Formula II or other formulas or compounds described herein can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmacological Sciences," Mack Publishing Co., Easton, PA., latest edition.

[0185] As used herein, "exposing," "administer" or "administration" refers to the delivery of a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof or of a pharmaceutical composition containing a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof of this invention to a mammal.

[0186] Suitable routes of administration may include, without limitation, oral, rectal, transmucosal or intestinal administration or intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, or intraocular injections. The preferred routes of administration are oral and parenteral.

[0187] Furthermore, one administer the compound in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor progenitor.

[0188] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0189] Pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0190] For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0191] For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl-pyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

[0192] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0193] Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers may be added in these formulations, also.

[0194] Pharmaceutical compositions which may also be used include hard gelatin capsules. As a non-limiting example, compound 1 in a capsule oral drug product formulation may be as 50 and 200 mg dose strengths. The two dose strengths are made from the same granules by filling into different size hard gelatin capsules, size 3 for the 50 mg capsule and size 0 for the 200 mg capsule.

[0195] The capsules may be packaged into brown glass or plastic bottles to protect the active compound from light. The containers containing the active compound capsule formulation must be stored at controlled room temperature (15-30°C).

[0196] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra- fluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0197] The compounds may also be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

[0198] Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection

suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0199] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

[0200] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

[0201] In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

[0202] A non-limiting example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer and an aqueous phase such as the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of such a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of Polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or polysaccharides may substitute for dextrose.

[0203] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

[0204] Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0205] The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0206]

Examples of formulations for use in the present invention are in Tables A-C:

TABLE A

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide hard gelatin capsules				
Ingredient Name	Concentration in Granulation (% w/w)	Amount in 50 mg Capsule (mg)	Amount in 75 mg Capsule (mg)	Amount in 200 mg Capsule (mg)
API	65.0	50.0	75.0	200.0
Mannitol	23.5	18.1	27.2	72.4
Croscarmellose Sodium^e	6.0	4.6	6.9	18.4
Povidone (K-25)	5.0	3.8	5.7	15.2
Magnesium Stearate	0.5	0.38	0.57	1.52
Capsule	-	Size 1	Size 3	Size 0

TABLE B

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules		
Ingredient Name/Grade	Concentration in Granulation (% w/w)	Amount in 50 mg Capsule (mg)
API	75.0	66.800^c
Mannitol	13.5	12.024
Croscarmellose Sodium^e	6.0	5.344
Povidone (K-25)	5.0	4.453
Magnesium Stearate	0.5	1.445
Capsule	-	Size 3

TABLE C

Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules				
Ingredient Name/Grade	Concentration in Granulation (% w/w)	Amount in 25 mg Capsule (mg)	Amount in 50 mg Capsule (mg)	Amount in 100 mg Capsule (mg)
API^a	40.0	33.400^d	66.800^c	200.0^b
Mannitol	47.5	39.663	79.326	158.652
Croscarmellose Sodium^e	6.0	5.010	10.020	20.04
Povidone (K-25)	5.0	4.175	8.350	16.700
Magnesium Stearate	1.5	1.252	2.504	5.008
Capsule	-	Size 3	Size 1	Size 0

^a Drug substance quantity required for the batch will be adjusted to have 100% of labeled strength for capsules. Appropriate adjustment will be made to mannitol quantity to keep the same fill weight for each strength.

^b Quantity equivalent to 100 mg free base.

^c Quantity equivalent to 50 mg free base.

^d Quantity equivalent to 25 mg free base.

^e Half intragranular half extragranular.

which can be found in U.S. Patent Application Serial No. 10/237,966, filed September 10, 2002, now a provisional application, which is expressly incorporated in its entirety by reference.

[0207] Many of the compounds of Formula I, Formula II or other formulas or compounds described herein may be provided as physiologically acceptable salts wherein the compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium, salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, malate, maleate, succinate wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted with the appropriate acid. Salts in which a compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), Calcium hydroxide (Ca(OH)₂), etc.).

[0208] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.*, a therapeutically effective amount.

[0209] Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0210] For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the IC₅₀ as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of phosphorylation of CSF1R). Such information can then be used to more accurately determine useful doses in humans.

[0211] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the IC₅₀ and the LD₅₀, wherein the LD₅₀ is the concentration of test compound which achieves a half-maximal inhibition of lethality, for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

[0212] Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from in vitro data, *e.g.*, the concentration necessary to achieve 50-90% inhibition of a kinase may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

[0213] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0214] At present, the therapeutically effective amounts of compounds of Formula I, Formula II or other formulas or compounds described in this application may range from approximately 25 mg/m² to 1500 mg/m² per day; alternatively about approximately 25 mg/m² to 1000 mg/m² per day. In another embodiment, the therapeutically effective amounts may range from approximately 25 mg/m² to 400 mg/m² per day.

[0215] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures known in the art may be employed to determine the correct dosage amount and interval.

[0216] The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

[0217] It is contemplated that the inventive method could be used in combination with other therapies, including chemotherapies, radiation therapies and surgical therapies for cancer. For combination therapies and pharmaceutical compositions described herein, the effective amounts of the compound of the invention and of the other agent can be determined by those of ordinary skill in the art, based on the effective amounts for the compounds described herein and those known or described for the other agent. The formulations and route of administration for such therapies and composition can be based on the information described herein for compositions and therapies comprising the compound of the invention as the sole active agent and on information provided for the chemotherapeutic and other agent in combination therewith.

[0218] Although all biomarkers disclosed in this specification are identified by specific sequences (and corresponding SEQ ID NOs), those skilled in the art will recognize that variants and alleles of these sequences also may function as biomarkers. Specific sequences, GenBank accession numbers and SEQ ID NOs in the specification are used to identify exemplary cDNAs, mRNAs and/or proteins of interest, and do not limit the invention to only those particular sequences. The biomarkers of the invention encompass variants and alleles of the disclosed sequences.

D. EXAMPLES – STUDIES USING COMPOUND A (SU6668)**1. Studies using Compound A – Materials and Methods****ELISAs**

[0219] Reagents for human tissue inhibitor of metalloproteinase 1 (TIMP-1), human active and pro-matrix metalloproteinase 9 (total MMP-9) and human vascular endothelial growth factor (VEGF) ELISA kits were obtained from R & D Systems, Inc. (Minneapolis, MN). Human plasminogen activator inhibitor-1 (PAI-1) and human tissue factor (TF) ELISA kits were obtained from American Diagnostica, Inc. (Greenwich, CT). All ELISAs were performed on plasma samples according to the manufacturers' instructions.

2D gel analysis

[0220] Patient plasma was analyzed by 2D gel electrophoresis by Kendrick Labs (Madison, WI) according to the method of O'Farrell (J. Biol. Chem. 250: 4007-4021, 1975). Briefly, 150 ug of plasma protein was separated by isoelectric focusing using pH 4-8 gradient IEF gels. A 10% SDS/PAGE gel was used for the second gel dimension. Limited computerized comparisons were carried out on duplicate silver-stained gels and the spot percentage was calculated according to the formula: Difference = (1-spot % sample x/spot % sample ref)(-100). Spots whose abundance appeared to differ after Compound A exposure were subsequently excised and MALDI-TOF analysis was carried out for identification purposes.

Isolation of RNA from whole frozen blood

[0221] TRI Reagent®BD – RNA, DNA, protein isolation reagent was used according to the manufacturer's protocol, Molecular Research Center, Inc. (Cincinnati, OH) <www.mrcgene.com>.

Transcriptional Profiling Using Affymetrix DNA Arrays

[0222] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/>

expression_manual.affx>. In brief, double-stranded cDNA was synthesized from total blood RNA (8 µg) of patient samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-(dT)₂₄ oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for in vitro transcription (IVT) of cRNA. The IVT reaction was performed using BioArray High Yield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station. Images were scanned with a Hewlett-Packard GeneArray scanner.

Data Analysis

[0223] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1000 for these experiments). For comparisons between time points from a single patient, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the post-treatment sample was divided by the AD of the pre-dose samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change ≥ 1.7 (increasing or decreasing).

TaqMan (qRT-PCR)

[0224] Primers and probes were designed using Primer Express 2.0 software, and purchased from Applied Biosystems (Foster City, CA). In all cases, primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). All probes contained a reporter dye (FAM) and a dye quencher (MGB). qRT-PCR was performed using 20 ng of total RNA with TaqMan® One-Step RT-

PCR Master Mix Reagents Kit (Applied Biosystems) following the manufacturer's protocol. The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. VEGF (Genbank accession number AF022375) transcripts were amplified using forward primer

GCTCTCTTATTGTACCGGTTTG (SEQ ID NO: 165), reverse primer

AAGCTAGTGACTGTCACCGATCAG (SEQ ID NO: 166), and probe

TCATGTTCCAATCTC (SEQ ID NO: 167) to generate an 82-bp amplicon product.

Vinculin (Genbank accession number M33308) transcripts were amplified using forward primer CCTGATATAAATGCAATATTAATGCCTTA (SEQ ID NO: 168), reverse primer AAGAACCGGGAGAGCAAACAT (SEQ ID NO: 169), and probe

ATCTATGCCAAAGATCACTT (SEQ ID NO: 170) to generate a 124-bp amplicon product.

PECAM-1 (Genbank accession number L34657) transcripts were amplified using forward primer GGAGCACCGCCTGTGAA (SEQ ID NO: 171), reverse primer

TGTGCGTTGCCTGAATGAAC (SEQ ID NO: 172), and probe ACCAACCTGAAGACAC (SEQ ID NO: 173) to generate a 56-bp amplicon product. MAPK Kinase 3 (Genbank accession number L36719) transcripts were amplified using forward primer

TCTCGACTGAATGGACTTGCA (SEQ ID NO: 174), reverse primer

TTGTGTACCCCGCACCAA (SEQ ID NO: 175), and probe CACACCTCTATCCCGGC (SEQ ID NO: 176) to generate a 77-bp amplicon product. Hemoglobin, epsilon 1 (Genbank accession number AI349593) transcripts were amplified using forward primer

GCTGCATGTGGATCCTGAGA (SEQ ID NO: 177), reverse primer

TGAGTAGCCAGAATAATCACCATCA (SEQ ID NO: 178), and probe

CTTCAAGCTCCTGGTAA (SEQ ID NO: 179) to generate a 66-bp amplicon product.

GAPDH and 18S were ordered as pre-developed assay reagents (PDARs) from Applied Biosystems and used as endogenous controls.

[0225] Data analysis of TaqMan (qRT-PCR): The Ct scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. The Ct scores for genes of interest for each sample were normalized against Ct scores for the corresponding endogenous control gene (GAPDH or 18S). Relative expression of specific transcripts in the post-dose sample compared to pre-dose sample was determined by the

following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} = 2^{-\Delta\Delta Ct},$$

Where $\Delta\Delta Ct = (Ct_{\text{target}} - Ct_{\text{control}})_{\text{post-dose}} - (Ct_{\text{target}} - Ct_{\text{control}})_{\text{pre-dose}}$.

2. Studies using Compound A – Results

ELISAs

[0226] Samples of plasma from human patients were taken before and 24 hours after the first dose of Compound A (SU6668). The patients were dosed twice over 24 hours with Compound A. The results of the ELISA analysis are shown in Figure 1, which shows that the levels of PAI-1, VEGF and TIMP-1 were increased in the plasma from patients exposed to Compound A. These proteins were therefore identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A. These patients were suffering from various types of cancer.

Two Dimensional Polyacrylamide Gel Electrophoresis

[0227] Samples of plasma from human patients suffering from advanced solid malignancies were taken before and 4 hours after the first (and only) doses of Compound A. A variety of proteins were increased and/or decreased in the plasma of patients treated with Compound A. As shown in Figures 2 and 3, mass spectrometry analysis identified one of these proteins (spot # 5) as ITIH4 (inter alpha (globulin) inhibitor H4). ITIH4 was therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A. See Figure 12 for sequences for ITIH4.

Microarrays and RT-PCR Analysis

[0228] Samples of whole blood from human patients suffering from advanced solid malignancies were taken before and 24 hours after the first dose of Compound A. An Affymetrix GeneChip analysis of the RNA transcripts present in patient blood before and after exposure to Compound A indicated that the levels of vinculin and VEGF RNA increase after exposure to Compound A (see Figure 4A and 4B). Vinculin and VEGF were therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A.

Microarrays and RT-PCR Analysis

[0229] Samples of whole blood from human patients were taken before and 27 days after the first dose of Compound A (in other words, samples were taken on day 0 and day 28; patients were dosed about 2 times per day on day 1-day 27, and following the first dose on day 28, the sample of blood was taken to measure biomarker(s). An Affymetrix GeneChip analysis of the RNA transcripts present in patient plasma before and after exposure to Compound A indicated that the levels of 26 transcripts were increased and/or decreased after exposure to Compound A (see Figure 5). Thus, 26 proteins/transcripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A: eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792), Homo sapiens thymosin beta-10, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, human KIAA0195, Homo sapiens MAP kinase kinase 3 (MKK3), human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA). See Figure 12 for sequences for these biomarkers.

E. EXAMPLES – STUDIES USING COMPOUND B (SU5416)

1. Studies using Compound B – Materials and Methods

Study Population

[0230] Patient samples were derived from 2 randomized, open-label, multicenter Phase III clinical trials comparing standard of care chemotherapy alone or combined with Compound B in patients with metastatic colorectal cancer. In both trials Compound B was delivered twice weekly at a dose of 145 mg/m² via I.V. infusion. In the first trial (designated Trial A), the standard of care chemotherapy consisted of weekly administration of 5-FU and leucovorin (Rosewell Park regimen); in the second trial (designated Trial B), the standard of care chemotherapy consisted of weekly or bi-weekly administration of 5-FU, leucovorin and

Irinotecan (CPT-11). A total of 23 patient sample pairs were included in Affymetrix microarray expression profiling analysis, 2 females and 9 males in the Compound B treatment arm, and 2 females and 10 males in the control arm. The median patient age was 66 and 65 years for the Compound B treatment arm and control arm, respectively. For RT-verification experiments, samples from 12 females and 24 males from the Compound B treatment arm, and 14 females and 17 males from the control arm were used. The median age for these patients was 62 and 60 years, respectively. Clinical response criteria were defined according to RECIST guidelines. Briefly, complete response (CR) is defined as complete disappearance of all measurable and evaluable clinical evidence of cancer; partial response (PR) is defined as at least a 50% reduction in the size of all measurable tumor areas; progressive disease (PD) is defined as an increase of $\geq 25\%$ (compared to baseline or best response) in the size of all measurable tumor areas; and stable disease (SD) is defined as neither sufficient shrinkage to quantify for PR nor sufficient increase to qualify for PD.

Patient samples

[0231] All clinical samples for biomarker analysis were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the study informed consent prior to any study related procedures. All blood samples were collected into Vacutainer tubes containing sodium heparin. Ten 10 ml of blood was withdrawn from patients prior to receiving any treatment on day 1 and also prior to dosing at end of cycle 1 (day 56 in Trial A; day 42 in Trial B). For peripheral blood mononuclear cell (PBMC) preparations, blood samples were shipped overnight at ambient temperature to a central processing facility (Quest Diagnostics, Inc., Collegeville, PA, USA) for PBMC isolation via Ficoll gradient method. Purified PBMCs were shipped in RNA lysis buffer (Clontech, Palo Alto, CA, USA) to SUGEN where isolation of total RNA was performed. For Trial B, whole peripheral blood samples were directly frozen at the clinical sites and shipped on dry ice to SUGEN for RNA isolation.

RNA sample processing

[0232] Total RNA was purified from PBMC samples using Clontech Nucleospin RNA II kit reagents (Clontech, Palo Alto, CA) and from whole blood samples using MRC

TRI Reagent BD (Molecular Research Center, Cincinnati, OH, USA), an adaptation of the Chomczynski single step method, according to the manufacturer's instructions. All sample preparations included a treatment with RNase-free DNase. RNA yields were measured by UV absorbance and RNA quality was assessed by agarose gel electrophoresis with ethidium bromide staining for visualization of ribosomal RNA band integrity.

Affymetrix high-density oligonucleotide microarray analysis of PBMC expression profiles

[0233] In general, the standard RNA processing and hybridization protocols as recommended by Affymetrix (Santa Clara, CA, USA) were followed in this study; these protocols are available in the Genechip® Expression Analysis Technical Manual (viewable at <www.affymetrix.com/support/technical/manual/expression_manual.affx>. Yields of total RNA for PBMC samples were generally low and for the majority of patients it was not possible to use the standard amount of total RNA ($\geq 5 \mu\text{g}$) as recommended in the standard protocol. Therefore a double linear amplification approach was used in the generation of cRNA for hybridization. In these experiments, equal amounts of starting material were used for pre- and post-treatment samples from each donor (typically 2 μg). Briefly, the protocol was as follows: double-stranded cDNA was synthesized from total RNA (2 μg), with Invitrogen Life Technologies SuperScript Choice system reagents (Invitrogen, Carlsbad, CA). The T7-(dT)₂₄ oligomer was used for priming first-strand cDNA synthesis. Double-stranded cDNA product was purified via phenol-chloroform extraction, then used as template in first round of in vitro transcription (IVT) of cRNA. The IVT reaction was performed with BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol but with substitution of non-biotinylated ribonucleotides for biotinylated ribonucleotides. The cRNA product was then purified with Qiagen spin column clean-up protocol and used as template in second round of cDNA synthesis. This second round of synthesis was similar to the first round except that random hexamers were used in priming of first-strand synthesis, with T7-(dT)₂₄ oligomer priming the second-strand. Purification of the cDNA was as in the first round. The second round of IVT of cRNA was as in the first round but with biotinylated ribonucleotides rather than non-biotinylated ribonucleotides. Purified cRNA was quantitated, chemically fragmented according to Affymetrix protocol, and then hybridized overnight on Human Genome U95A Arrays (which contain probe sets for the detection of approximately 12,600

transcripts). Hybridized arrays were washed and stained with phyoerythrin-conjugated strepavidin detection chemistry in an Affymetrix Fluidics station, then images were scanned with a Hewlett-Packard GeneArray scanner.

Data Analysis

[0234] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The key output from individual arrays are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays. Average Difference determination relies on difference between background-subtracted signal from perfect match (PM) oligos and corresponding mismatch control (MM) oligos within a probe set representing a given transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a Scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (which was set at 1500 for these experiments). For comparisons between time points from a single patient, batch files were generated with Microarray Suite. These files contain calculated fold change (FC) values, which represent differential expression ratios of day 56 compared to baseline, and also Difference Calls (DC), which represent a more conservative estimate of differential expression, with qualitative scores assigned to each transcript measurement according to the following system: Increased (I), Marginally Increased (MI), No Change (NC), Marginally Decreased (MD), and Decreased (D).

[0235] Subsequent data analysis was performed primarily with Spotfire DecisionSite for Functional Genomics software (version 7) package and its Array Explorer component (Spotfire, Somerville, MA). Hierarchical clustering analysis and statistical comparisons were included in this step. Further refinement of the data, including filtering by Difference Call scores, was done with the Microsoft Access 97 database analysis program.

SYBR Green quantitative RT-PCR verification of array results

[0236] Primers were designed with Primer Express 1.5 software (Applied Biosystems). In all cases, primers were designed to bind within the sequence that was used in Affymetrix probe set designs (target sequence information available on Affymterix NetAffx website). Total RNA samples (1 µg) were reverse transcribed to yield first-strand cDNA using the Applied Biosystems Reverse Transcription Reagents protocol (Applied Biosystems, Foster City, CA). The reverse transcription reactions were then diluted 1:5 in distilled H₂O.

SYBR Green PCR reactions were performed in 96-well optical plates and run in an ABI PRISM® 7700 Sequence Detection System (SDS) machine. For individual reactions, 10 µl of each sample were combined with 15 µl of SYBR Green PCR Master Mix (Applied Biosystems) containing the appropriate primer pair at 350 nM. Data was extracted and amplification plots generated with ABI SDS software. All amplifications were done in duplicate and threshold cycle (C_t) scores were averaged for subsequent calculations of relative expression values. The C_t scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. Heat dissociation curve analysis was performed after each SYBR Green run as a test of whether a single product had been generated in each PCR reaction; multiple peaks in the dissociation curves are indicative of multiple PCR products and thus reduced specificity and sensitivity.

Quantitation and statistical analysis of SYBR Green PCR data

[0237] The C_t scores for genes of interest for each sample were normalized against C_t scores for the corresponding endogenous control gene, which was the β -glucuronidase (GUS) gene in these experiments. Relative expression for day 56 compared to day 1 was determined by the following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} = 2^{-\Delta\Delta C_t},$$

Where $\Delta\Delta C_t = (C_{t \text{ Target}} - C_{t \text{ GUS}})_{\text{day 56}} - (C_{t \text{ Target}} - C_{t \text{ GUS}})_{\text{day 1}}$.

[0238] The relative expression data for a select subset of potential biomarkers were tested for differences between the Compound B (treatment) and the standard of care (control) arms. The Mann-Whitney U Test with a critical alpha level of 0.05 was used for statistical significance. Individual genes observed to be significantly different by Affymetrix analysis and in both sets of SYBR Green RT-PCR experiments were screened as potential biomarker candidates. This subset of potential biomarker candidates was tested subsequently for utility as class predictors to discriminate between the Compound B and standard of care arms. Discriminant analysis, a multivariate statistical technique, was used for this purpose. The genes were tested individually, using all possible combinations, by reducing dimensions (Principal Component Analysis) in order to determine the subset of genes (predictor variables) that yielded highest classification accuracy. Cross-validation was used to test the robustness of classification accuracy. Results from three different cross-validations were evaluated to select the best set of predictable biomarkers: (1) jackknife method (dropping

one case at a time); (2) randomly splitting the pooled data into two halves, prediction (for building model) and validation (for testing model); and (3) using the first trial as prediction and the later trial as validation sets, respectively. All statistical analyses were carried out after natural-log transformation on the data; SYSTAT 9.01 (SPSS, Inc., Chicago, IL, USA) software was used in statistical analysis.

2. Studies using Compound B – Results

Affymetrix expression profiling of pre- and post-treatment matched PBMC samples

[0239] Expression profiling using Affymetrix high-density oligonucleotide microarrays was applied to PBMC samples harvested from patients in a Phase III clinical trial of Compound B in Trial A. The PBMC samples were harvested at baseline (day 1) and at end of cycle 1 (day 56) from patients receiving standard-of-care (5-FU/leucovorin) treatment and from those receiving standard-of-care plus Compound B. Sample pairs from 23 patients were processed and the dataset was filtered for expression changes that consistently correlated with the treatment arm (Compound B). Of 13 genes that met the initial requirement, 6 were further tested by quantitative RT-PCR analysis of additional patient samples from patients.

[0240] Table 1 includes a summary of the total samples processed. As RNA yields rarely exceeded 2 µg, a double amplification step was used in cRNA generation for the samples that were used (see Materials and Methods). Only samples from patients with cycle 1 responses of either PR/CR or PD were used in the final dataset.

[0241] Batch comparison files were generated for each day 1/day 56 sample pair after hybridization. Batch comparisons included both fold change (FC) values as calculated by Affymetrix Microarray Suite software as well as difference calls (DC). DC offer a more stringent but non-numerical measure of whether levels of a transcript are different in the 2 samples. Batch comparison results for the 23 cases were analyzed with Spotfire Decision Site software tools. Initial analysis suggested there was more similarity among patient samples of the same treatment arm than among samples of the same response category (PR/CR or PD) independent of treatment arm. Therefore, subsequent analysis focused on identification of transcripts that were differentially expressed in the Compound B arm but not in the control arm.

[0242] The Treatment Comparison tool in Spotfire was used to identify transcripts that were statistically significantly different in the two treatment arms; this tool uses t-test analysis of averaged fold changes for each group. To further refine this subset of genes, queries based on DC status were performed with Microsoft Access. The data were filtered to identify those genes that were called ‘Increased’ (I) or ‘Decreased’ (D) in a majority of the Compound B arm cases. A group of 13 genes that frequently showed increased expression was identified. Figure 6 displays a schema of the DC scores assigned to each gene for each patient sample pair. All cases from the Compound B arm show induction in at least 6 of the 13 genes.

[0243] Table 2 includes a brief summary of putative biological function for each of the 13 gene products, as well as an ID number assigned by Affymetrix to each transcript-specific probe. The last two columns in Table 2 list the number of patients in which transcript levels were increased at day 56 relative to day 1 (i.e., an ‘Increase’ call was assigned). Total number of patients is 11 for the Compound B (SU5416) arm and 12 for the control arm. The average fold change of all of these transcripts was higher in the Compound B (SU5416) arm (the lowest average fold change was 2.6 for hypothetical protein FLJ13052, the highest was 33 for lactoferrin); the range of fold changes was also broader in this category, presumably representing variability among patients.

Quantitative RT-PCR validation of differentially expressed transcripts

[0244] To validate the microarray results, a subset of these transcripts was chosen for quantitative RT-PCR analysis. Primer sets were designed for 6 of the 13 genes; matrix metalloproteinase-9 (MMP-9), thrombospondin-1 (TSP-1), CD24, defensin α 3, lipocalin 2 (LCN2), and lactoferrin. These 6 genes were chosen based on potential roles of encoded proteins (for example, thrombospondin-1 and MMP-9 have known roles in angiogenesis) or because of the degree to which they appeared to be differentially regulated between treatment arms. The lipocalin-2 gene (LCN2) has been reported to be inducible by dexamethasone (Science, 293: 829-34 (2001)). Dexamethasone is one of the premedications administered to patients in the Compound B arm. Table 3 describes the forward and reverse primers that were used in validation of these transcripts.

[0245] SYBR Green chemistry was used to validate the microarray expression profiling data. SYBR Green is a dye that fluoresces when bound to double-stranded DNA,

thus signal is directly proportional to the amount of product formed during PCR amplification. This method allows rapid and inexpensive comparison of gene expression across a large number of samples. The qRT-PCR validation was performed with a total of 31 Compound B patient sample pairs, 8 of which had previously been analyzed on Affymetrix U95A arrays and thus allowed a comparison of the correlation between the 2 transcript profiling methods. Of the 31 samples, 18 were from the Compound B arm and 13 were from the control arm.

[0246] Data for each gene was normalized to expression of a housekeeping gene, β -glucuronidase (GUS). By direct comparison of SYBR Green RT-PCR results and Affymetrix results from the same cases, the overall qualitative correlation (i.e., same trend of induction or no change detected in both samples) was greater than 70%. This number is perhaps an underestimate since results for one patient were completely discordant between methods and thus potentially due to experimental artifact.

[0247] Figure 7 summarizes the results from the RT-PCR validation and compares them with those from the Affymetrix analysis. It is clear that there are some differences in the trends displayed in the 2 datasets. This is further demonstrated by statistical analysis, as Mann-Whitney U test comparison of Compound B and control results from both analyses indicates that only 4 of the 6 genes display statistical significance (Table 4). These 4 genes are CD24, lactoferrin, LCN2, and MMP-9. (MMP-9 exhibited a p-value that was close to the significance cutoff and thus was also selected for further analysis.)

Qualitative RT-PCR validation of differentially expressed transcripts with samples from a second Phase III Compound B trial

[0248] To further confirm these transcripts as biomarkers of Compound B administration, SYBR Green RT-PCR analysis of these 4 transcripts was carried out in a collection of samples from a second Phase III trial (Trial B). In this randomized metastatic colorectal cancer study, 5-FU/leucovorin/CPT-11 was administered as the standard of care, and compared to the standard of care plus Compound B. RNA samples from patients in this trial were derived from frozen whole blood (rather than purified PBMCs), and harvested at the beginning (pre-dose day 1) and at the end (day 42) of cycle 1. To test if similar results occurred, analysis was performed on 36 sample pairs, 18 from Compound B arm and 18 from control arm. Due to limited numbers of available samples, many of the cases analyzed in this

analysis were from patients with stable disease (SD) at cycle 1 assessment rather than PR/CR and PD as in the previous approaches.

[0249] Figure 8 summarizes the overall behavior of the transcript levels in both trial arms in terms of the frequency with which the transcripts showed an induction (here defined as relative expression, day 42 vs day 1) of 2-fold or greater in each arm. It is clear that there is more induction of these transcripts at day 42 in the Compound B arm than in the control arm. This is also reflected in statistical analysis, as indicated in results of the Mann-Whitney U Test of this dataset (Table 5).

[0250] A visual representation of hierarchical clustering analysis of the qRT-PCR relative expression values from both trials for each of the transcripts is displayed in Figure 9. This clustering pattern displays the distinction between the Compound B and control arms based on relative expression data, and also indicates further distinctions among subsets of patients as well as the degree of overlap between trial arms in the clustering pattern. The extent of similarity between the relative expression patterns for each transcript (represented in columns) is also indicated; the pattern of MMP-9 is distinct from the others as it appears in a separate branch in the dendrogram structure.

Discriminant analysis of the classification power of biomarkers

[0251] We tested whether relative expression data from these samples could be used in a predictive fashion to classify samples to the appropriate trial arm. To test this, discriminant analysis of the SYBR Green RT-PCR data was performed. Relative expression values from both the first and the second dataset were combined, after comparison of mean relative expression ratios and standard deviations indicated greater similarity between respective trial arms rather than between control and Compound B arm in either trial alone. The relative expression ratios were then natural log-transformed to reduce the scale of the values and thus make control and treated arms more comparable. When the samples were pooled (67 cases altogether) and subjected to classification prediction, a total prediction accuracy of 84% was achieved. Further cross-validation was performed by the jack-knife method (which does a series of predictions, randomly removing 1 case from the total each time), and by splitting the data set into 2 random halves (one a ‘training’ set and the other a ‘testing’ set).

[0252] The results from each of these steps are summarized in Table 6 for a set of 3 of the 4 transcripts that gave the best accuracy percentage (including MMP-9 slightly reduced the accuracy of cross-validation). Thus, it is predicted that expression data from these 3 genes would accurately distinguish Compound B arm patients from control arm in between 67% to 84% of cases. When the first trial data was used as the ‘training’ set and the second trial data as the ‘testing’, as opposed to randomly selecting the data, the % accuracy in cross-validation was 86% and 77% for the training and testing set, respectively. Cross-validation results are displayed for two different approaches. In section 2 of Table 6, one case is dropped at a time and its group membership predicted from the other cases. In sections 3 and 4, cross-validation is carried out by using a randomly selected half of the cases as a training set and the remaining half as a test set. Section 4 summarizes the prediction accuracy achieved when the group in section 3 is used as a training set.

Conclusions: Compound B Studies

[0253] Large-scale gene expression analysis was applied to blood RNA samples from a clinical trial of Compound B to investigate changes in gene expression that might correlate with exposure to cancer therapy. Independent quantitative RT-PCR validation of initial array hybridization results was performed on larger sample populations from two conceptually similar Phase III clinical trials using Compound B. A set of 4 transcripts (CD24, lactoferrin, LCN2, and MMP-9) was identified whose expression was significantly induced at the end of one treatment cycle relative to baseline following Compound B administration. Discriminant analysis indicates that data derived from the RT-PCR study would have a class prediction accuracy of at least 70%.

[0254] These 4 transcripts are considered to be biomarkers of Compound B administration and other compounds that inhibit tyrosine kinase. These results also demonstrate that human blood samples can serve as surrogate tissues for biomarker investigations and that large-scale gene expression analysis is a useful approach for characterization of clinical trial samples.

F. EXAMPLES – FURTHER STUDIES USING COMPOUND B (SU5416)**Baseline and post-treatment levels of PAI-1 in Compound B patient plasma**

[0255] PAI-1 plasma levels were examined in samples from Compound B patients. Interestingly, median PAI-1 levels decreased after 56 days of treatment in samples from all patients examined with a MR (minor response) at the end of cycle 1 (Figure 10, n = 37; Compound B arm day 1 median 40.66 ng/ml, day 56 median 23.93 ng/ml, 5FU/LV arm day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml). In contrast, median PAI-1 levels in samples from all patients examined with a PD (progressive disease) response at the end of cycle 1 did not appear to change significantly (Figure 10, n = 47; Compound B arm day 1 median 26.47 ng/ml, day 56 median 34.8 ng/ml, 5FU/LV arm day 1 median 25.67 ng/ml, day 56 median 23.29 ng/ml). Furthermore, the decrease in PAI-1 plasma levels in the control arm MR patients after 56 days of treatment was statistically significant (day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml, P = 0.0003; n = 20). The decrease in PAI-1 levels of Compound B arm patients was not statistically significant (P = 0.095; n = 17). These data indicate that changes in plasma PAI-1 levels after one cycle of treatment correlate with cycle one clinical response of both the experimental and control arm regimens.

Pre-treatment levels of PAI-1

[0256] An analysis of the pre-treatment plasma levels of plasminogen activator inhibitor-1 (PAI-1) shows that pre-treatment levels also correlate with clinical response (on day 56) in either arm, indicating that PAI-1 is a biomarker predictive of response to tyrosine kinase inhibitor in advanced colorectal cancer.

[0257] An analysis of the pre-treatment levels of PAI-1 indicated that patients with an MR response (cycle 1) had a statistically significantly (P = 0.001) higher level of plasma PAI-1 (median 41 ng/ml; n = 37) than that of patients with a PD response (median 26 ng/ml; n = 47) regardless of the regimen subsequently received. Thus far, only 4 patients that had a partial response (PR) at the end of cycle 1 have been examined for PAI-1 plasma levels. These patients have pre-treatment levels (median 37.4 ng/ml) similar to the MR patients (median 40 ng/ml), however PAI-1 levels did not decrease significantly in these patients samples after 56 days of treatment. These results (see Figure 10) indicate that the pre-treatment levels of plasma PAI-1 are predictive of MR response (as compared to a PD response) to either the experimental or the control arm regimen.

[0258] The present invention includes a method for predicting the probability of whether a patient will respond positively to administration of a tyrosine kinase inhibitor, comprising measuring the level of PAI-1 in patient plasma, wherein a level of greater than 30 nanograms/per ml of plasma, or greater than at least 35 nanograms, or greater than at least 37 nanograms per ml, indicates a positive probability that the patient will respond positively to administration of a tyrosine kinase inhibitor.

G. EXAMPLES – STUDIES USING COMPOUND 1

1. Studies using Compound 1 – Materials and Methods

[0259] A panel of proteins were investigated for their utility as biomarkers of Compound 1 in cancer patients receiving the compound in Phase I trials. The patient samples were from a total of four Phase I trials, 3 of which were open to patients with any advanced solid malignancy (these were Trials A, B and C) and one of which (Trial D) was a trial in patients with Gleevec-refractory, resistant, or intolerant gastrointestinal stromal tumors (GIST). In all cases, plasma samples were available from just before first Compound 1, or malate salt thereof, dose (baseline) and at various time points during dosing. In Trials A and B, patients received Compound 1. In Trials C and D, patients received a malate salt of Compound 1. For methods of making Compound 1, see U.S. Ser. No. 09/783,264 or WO 01/60814, U.S. Ser. No. 10/076,140 or U.S. Ser. No. 10/281,985, the disclosures of which are incorporated by reference. For methods of formulating Compound 1, see U.S. Ser. No. 10/237,966 (now a U.S. provisional application), the disclosure of which is incorporated by reference.

[0260] All of the ELISA-based screening of candidate proteins were performed with commercially available ELISA kits; the kits for the biomarkers described in this report are all available from R&D Systems (Minneapolis, MN). A commercially available membrane array containing antibodies for the detection of 42 human cytokines was also used in screening of a patient's plasma samples before and after treatment. The antibody array used in cytokine screening (RayBio Human Cytokine Array III) was from RayBiotech (Norcross, GA).

[0261] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol. Study participants signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood

samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site. The time points for which plasma samples are available in each trial are as follows:

Trial A (4 weeks on/ 2 weeks off dosing schedule):
plasma – Day 1 (0, 6, 24 hr); Day 28 (0, 6, 24 hr)

Trial B (2 weeks on/ 2 weeks off):
Plasma – Day 1 (0, 6, 12, 24 hr); Day 13 (0, 6, 12, 24 hr)

Trial C (4 weeks on/ 2 weeks off):
Plasma – Day 1 (0, 6 hr); Day 15, 29, 42* (Cycle 1); Day 1, 15, 29 (Cycle 2)

Trial D (2 weeks on/ 2 weeks off):
Plasma – Day 1, 7, 14, 28* (Cycle 1); Day 1 only, in subsequent cycles

Trial E (4 weeks on/2 weeks off):
Plasma – Day 1, 3, 28 (Cycle 1)

* ‘washout’ sample

Plasma samples were also collected from a set of 10 SUGEN healthy donors; plasma was collected at 3 time points for each donor (day 1, 14, and 28) to mimic time points used in the Phase I trials and thus serve as controls for the normal level of fluctuation of plasma markers in the absence of Compound 1 treatment.

[0262] Data analysis was performed for each marker. This was done by generating ratios of plasma levels at various time points during treatment versus the plasma levels at baseline (pre-dose on day 1, cycle 1), or by comparing absolute plasma concentrations at times during treatment to the baseline absolute plasma concentrations. For correlative analysis, scatter plots were drawn and linear regressions were calculated comparing fold change (end of cycle 1 dosing to baseline) of each marker to corresponding values assigned to clinical parameters such as pharmacokinetics, drug dosage, and ¹⁸FDG-PET functional imaging.

2. Studies using Compound 1 – Results

[0263] A panel of candidate proteins was evaluated by ELISA analysis in plasma samples from cancer patients receiving Compound 1 or malate salt thereof. Of those investigated, a subset was observed to change consistently in patients receiving Compound 1 or malate salt thereof. One of the proteins was Vascular Endothelial Growth Factor (VEGF);

large increases (greater than 3-fold) in plasma levels were seen in approximately 70% of patients in Trials A, B and C, and in a small proportion of patients in Trial D.

[0264] Figure 13 displays typical pattern of VEGF plasma levels seen in Trial C. VEGF levels are observed to rise by day 15 of cycle 1 and typically peak at day 29, then tend to subside to near baseline levels by day 42, which is the end of the 2-week drug rest period, or ‘washout’, in these patients.

[0265] To further investigate this, levels of a related angiogenic factor, Placenta Growth Factor (PLGF), were measured in some of the same patients as in the VEGF tests. As shown in Table 7, levels of PLGF are induced in a majority of patient samples that were tested, and follow a similar pattern as VEGF in that levels are most induced at day 29 and decline by day 42.

[0266] A further question regarding VEGF and PLGF was whether the presence of VEGF/PLGF heterodimers in patients’ plasma could be detected, and whether levels of the heterodimer could be modulated by treatment with Compound 1 or malate salt thereof. Heterodimers of VEGF and PLGF have been reported in the scientific literature. To measure heterodimers, a hybrid ELISA assay was used, combining reagents from both the R&D Systems VEGF and PLGF ELISA kits (where VEGF antibodies are used in capture step and PLGF antibodies are used in detection step).

[0267] The results of applying this assay to plasma samples from 3 patients are shown in Figure 14. Data from the same samples for VEGF and PLGF are also shown in the graphs in Figure 14. A similar pattern of induction of the VEGF/PLGF heterodimer as was seen for VEGF and PLGF was observed. In 3 of 3 patients tested, an increase in plasma levels of VEGF/PLGF heterodimer is observed, indicating that both PLGF and the VEGF/PLGF heterodimer are novel biomarkers of Compound 1 activity in patients.

[0268] Another protein, VEGF receptor 2 (VEGFR2) was investigated. VEGFR2 is one of the targets of Compound 1 and is important in angiogenesis. Whether soluble VEGFR2 is detectable via ELISA in plasma samples from cancer patients was investigated, as well as whether levels of the protein would change in response to treatment with Compound 1 or malate salt thereof.

[0269] Intriguingly, levels of the plasma soluble form of VEGFR2 were observed to decrease in the vast majority of patients (greater than 90%) in Trials A, B and C at chronic time points (13 days or more) after the start of treatment with Compound 1 or malate salt

thereof. Also, in Trial D, a dose-dependency of the sVEGFR2 decrease was seen, as changes were clearly observed in a cohort of patients in that trial receiving 50 mg daily doses of a malate salt of Compound 1, but not observed in a cohort of patients receiving 25 mg daily doses (Figure 15). The difference between the dose cohorts was statistically significant as judged by t-test. Also, levels of sVEGFR2 typically increased to near baseline levels at the end of the 2-week drug rest period in patients from all 4 trials, thus exhibiting a pattern similar in timing but opposite in direction to that seen for VEGF and PLGF (Table 9). Table 9 displays results for sVEGFR2 in individual patients, and also includes results for PLGF where available. Also included in Table 9 is information on the types of cancers found in the patients.

[0270] Further, data suggests that there exists some correlation between the extent of decrease in plasma sVEGFR2 and pharmacokinetics measurements of drug exposure in patients. This is demonstrated in Figure 16, which shows a scatter graph plotting change in sVEGFR2 plasma level (ratio of level on last day of cycle 1 dosing to baseline level) against area under curve (AUC) drug exposure measurements (from last day of cycle 1 dosing). The graph is a composite of data from all 4 trials, and the R-squared value indicates there is some association between decrease in sVEGFR2 and drug exposure. Thus, soluble VEGFR2 is a novel marker of Compound 1 treatment and may be a marker of both drug exposure and biological activity of the compound.

[0271] Another potential biomarker of Compound 1 was identified first in an array-based screen of plasma samples, before and after Compound 1 treatment, from a patient in Trial B. The array screen utilized a commercially available antibody membrane array, which in principle allows for simultaneous measurement of 42 different human cytokines. Results of the screen indicated that levels of a protein called Monokine Induced by Interferon-gamma, or MIG, were significantly higher after treatment with Compound 1 than in baseline samples. This result was confirmed via an MIG ELISA assay on the same patient samples. Following confirmation, levels of MIG in plasma were assessed for a number of patients from Trial C. These results showed that MIG was induced more than 3-fold in 30-40% of the patients tested (data not shown).

[0272] There is evidence of a correlation between increased MIG levels and a positive response in the functional imaging assay of ¹⁸FDG-PET (a feature of Trials C and D). This is illustrated in Figure 17; those patients with at least a mixed response based on PET imaging tended to have higher folds of induction of secreted MIG protein. To further

investigate the induction of MIG observed in patients, we have also measured the plasma levels of IP-10 and I-TAC before and after treatment with Compound 1 or malate salt thereof. IP-10 and I-TAC, like MIG, are regulated at the expression level by interferon-gamma, and both IP-10 and MIG have roles in chemoattraction of immune cells and exhibit angiostatic (anti-angiogenic) activity. Interestingly, evidence suggests that MIG and IP-10 are induced in tandem in 6 of 6 patients checked for both proteins while MIG and I-TAC are induced in tandem in 5 of 5 (Table 8). Similarly, all 3 proteins are induced in the 2 patients where all of the 3 were checked (Table 8). Table 10 indicates the types of cancer found in patients where MIG is induced. Thus, evidence indicates that MIG, IP-10 and I-TAC are novel biomarkers that are modulated in Compound 1 patients and are markers that correlate with an anti-tumor response as measured by PET imaging.

[0273] In summary, ELISA-based screening of plasma samples from Phase I clinical trials using Compound 1, or malate salt thereof, has yielded a set of circulating proteins that are novel surrogate markers for Compound 1 drug exposure and/or biological activity. Soluble VEGFR2 has been identified in plasma as a marker of drug exposure, while VEGF, PLGF, and VEGF/PLGF heterodimers have been frequently observed to increase in a majority of patients and appear to be correlates of biological activity and (to a lesser extent than sVEGFR2) drug exposure. MIG, IP-10 and I-TAC are additional biomarkers that appear to correlate with anti-tumor activity as measured by ^{18}FDG -PET functional imaging.

H. EXAMPLES – FURTHER STUDIES USING COMPOUND 1

1. Further studies using Compound 1 – Materials and Methods

In Vivo Animal Studies

[0274] Female athymic-*nu/nu* mice (Charles River, Hollister, CA) were injected with Colo205 human colon cells (5×10^6 cells) subcutaneously. The animals were treated with a single dose of either citrate vehicle or Compound 1 at 40 mg/kg when the tumors are approximately 350-400 mm³ in size. For biomarker studies, tumors were harvested at six and 24 hours post-treatment and snap frozen for RNA extraction.

Transcriptional Profiling Using Affymetrix DNA Arrays

[0275] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual
<www.affymetrix.com/support/technical/manual/expression_manual.affx>. In brief, total RNA from tumor samples was prepared using Nucleospin RNA II Kit in accordance with the manufacturer's recommendation (Clontech, Palo Alto, CA). RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual
<www.affymetrix.com/support/technical/manual/expression_manual.affx>. In brief, double-stranded cDNA was synthesized from total RNA (8 µg) of tumor samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-(dT)₂₄ oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for *in vitro* transcription (IVT) of cRNA. The IVT reaction was performed using BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station.

Images were scanned with a Hewlett-Packard GeneArray scanner. All techniques were performed on xenograft tissue samples according to the manufacturers' instructions.

Data analysis of DNA microarray

[0276] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1500 for these experiments). For comparisons between different treatments from a single time point, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the drug-treated samples was divided by the AD of the vehicle-treated samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change ≥ 2.0 (increasing or decreasing).

Taqman Real-Time RT-PCR Assay

[0277] Primers and probes were designed using Primer Express 2.0 software (Applied Biosystems, Foster City, CA). All primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). Taqman probes were labeled with reporter dye, 6-carboxy-fluorescein phosphoamidite (FAM), at the 5' end and dye quencher, minor groove binder (MGB), at the 3' end. Each 25- μ l reaction consisted of 500 nm forward primer, 500 nm reverse primer, 100 nm of Taqman probe, cDNA (20 ng of total RNA from tumor samples), and 1X (final concentration) of Taqman® One-Step RT-PCR Master Mix Reagents Kit (Applied Biosystems). The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. 18S ribosomal gene's primers and probe pairs were purchased from Applied Biosystems and used according

to manufacturer's recommendation as an endogenous control. All techniques were performed on the tissue samples according to the manufacturers' instructions.

Data analysis of Taqman assay

[0278] The Ct scores represent the cycle number at which fluorescence signal (ΔR_n) crosses an arbitrary (user-defined) threshold. The Ct score for genes of interest for each sample were normalized against Ct score for the corresponding endogenous control gene (18S). Relative expression of specific transcripts in the drug-treated sample compared to vehicle-treated sample was determined by the following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Relative Expression} = 2^{-\Delta\Delta C_t},$$

where $\Delta\Delta C_t = (Ct_{\text{target}} - Ct_{18\text{s control}})_{\text{drug treatment}} - (Ct_{\text{target}} - Ct_{18\text{s control}})_{\text{vehicle treatment}}$.

2. Further Studies using Compound 1 – Results

Microarrays and RT-PCR Analysis

[0279] To identify biomarker(s), samples of tissue from the tumors were taken before and after the first dose of Compound 1. An Affymetrix GeneChip analysis of the RNA transcripts present in xenograft tissue before and after exposure to Compound 1 indicated that the levels of 28 transcripts increased and/or decreased after exposure to Compound 1 (see Table 11A and 11B). Thus, the following 26 proteins/trasnscripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound 1: basic transcription factor 3 homologue, human c-jun proto-oncogene, human c-fos proto-oncogen, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, vinculin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, gelsolin and cyclin D2. See Figure 24 for sequences for these biomarkers.

[0280] To validate the Affymetrix GeneChip results, a subset of 11 of these 26 transcripts was chosen for quantitative RT-PCR analysis. These 11 transcripts were chosen

based on potential roles of encoded proteins. Table 13 describes the forward and reverse primers that were designed and used in the RT-PCR experiments. The results of the quantitative RT-PCR analysis for these 11 transcripts are shown in Table 12. The RT-PCR analysis confirms the findings with the Affymetrix GeneChip analysis for these 11 transcripts.

I. EXAMPLES – ADDITIONAL STUDIES USING COMPOUND 1

1. Additional studies using Compound 1 – Materials and Methods

Human Umbilical Vein Endothelial Cells (HUVECs)

[0281] HUVECs were obtained from Clonetics (San Diego, CA catalog# CC-2517) and were maintained in EGM media (Clonetics, catalog# CC-3121) containing EGM BulletKit (Clonetics, catalog# CC-4133: 2% Fetal Bovine Serum, 0.1% Epidermal Growth Factor, 0.1% Hydrocortisone, 0.1% Gentamicin Sulfate Amphotericin B, 0.4% Bovine Brain Extract). Cells were propagated at 37°C in a humidified atmosphere of 5% CO₂ using standard cell culture techniques. Cells were plated in 10-cm tissue culture plates at 8.5 X 10⁵ cells/ml. After 6 hours the cells were quiesced by serum starvation overnight in starvation medium (EBM containing 0.5% FBS). DMSO (Sigma Chemicals, St. Louis, MO #D2650) or Compound 1 (to a final concentration of 10 nM, 100 nM, and 1 μM) were added to cells. After 2 hours of exposure to Compound 1 or DMSO, VEGF₁₆₅ (R&D Systems, Minneapolis, MN; catalog# 293VE050) was added to a final concentration of 100 ng/ml; no VEGF was added to samples that are subsequently referred to as the “baseline” samples. After a 10-min, 8 hr, 24 hr and 48h VEGF stimulation the conditioned medium was filtered through 0.45 μM syringe filter from Pall Gelman Laboratory (Ann Arbor, MI catalog# 4560) and immediately frozen on dry ice. Conditioned media was stored at -70°C until subsequent analysis.

Analysis of Conditioned Media by 2D gel electrophoresis

[0282] Thawed conditioned media samples were precipitated with three volumes of acetone for 2 hours at -20°C, then centrifuged at 13000 RPM for 15 minutes. Pellets were washed with the 2D Clean-Up Kit (Amersham, Cat. # 80-6484-51) as per protocol, air dried for three minutes, then resuspended in 8M urea (Amersham), 100 mM dithiothreitol (Fisher), 4% CHAPS (3[(cholamidopropyl)dimethylammonio]propanesulfonate from Calbiochem), and placed in a thermomixer (Eppendorf) at 600 RPM and 25°C for 2 hours. Protein was quantitated with Bio-Rad Protein Assay (cat# 500-0006) using the microassay for cuvettes protocol.

[0283] Samples were diluted to 0.3 μg/μl with IEF Buffer containing 1% IPG Buffer pH 3-10 (Amersham). Eighteen centimeter IPG strips pH 3-10 (Amersham) were rehydrated with 120 μg sample (400 μL) under Drystrip Cover Fluid (Amersham) on the IPGphor (Amersham) at 20°C for 18 hours. Strips were focused with the following program:

200 volts for 1 hour, ramped from 200 volts to 1000 volts over two hours, held at 1000 volts for 1 hour, ramped from 1000 volts to 8000 volts over 6 hours, then held at 8000 volts for 10 hours. Polyacrylamide gels were hand cast in the Hoeffer DALT multi-gel casting chamber (Amersham) at 10% Acrylamide (Bio-Rad 40% Acrylamide Solution), 2.67% piperazine diacrylamide (Bio-Rad), 0.375 M tris, pH 8.8 (Bio-Rad), 0.075% ammonium persulfate (Bio-Rad), and 0.075% TEMED (N, N, N', N'-tetramethylethylenediamine). Gels were overlayed with water-saturated butanol (Fisher), and left to polymerize at room temperature overnight.

[0284] Focused strips were equilibrated for ten minutes with gentle shaking in 10 milliliters Equilibration Buffer: 6 M Urea (Fisher), 50 mM tris-HCl pH 8.8 (Fisher), 30% glycerol (Fisher), 2% SDS (Fisher) with 1% dithiothreitol followed by ten minutes in Equilibration Buffer with 4% iodoacetamide.

[0285] The equilibrated strips were loaded onto the gel surfaces and sealed with hot agarose overlay solution containing 0.5% agarose in 50 mM tris-HCl pH 6.8, 2% SDS.

[0286] Gels were run in the Hoeffer DALT tank (Amersham) in 25 mM tris (Fisher), 192 mM glycine (Fisher), and 0.1% SDS overnight at 100 volts and 8°C.

[0287] The gels were washed three times in 500 mL Fixative (10% methanol and 7% glacial acetic acid) for one hour each with gentle agitation. The gels were then stained overnight in 500 mL Sypro Ruby Protein Gel Stain (Molecular Probes). Gels were again washed three times in 500 mL fixative for an hour each with gentle agitation. Images were obtained on the Fluor S MultiImager (Bio-Rad) using transilluminated ultraviolet light for 45 seconds with the 520LP emission filter. Image analysis was done using PDQuest version 7.0.1 (Bio-Rad).

2D Gel Spot Cutting

[0288] The automated gel cutting was performed using the ProteomeWorks Spot Cutter (BioRad, Hercules, CA) and PDQUEST (v.7.0.1) software. Three sets of 2D gels were cut (Table 14). Based on the gel imaging analysis, the same spots of all three gels were combined in the same well of a 96-well plate.

Protein In-gel Digestion

[0289] The automated digestion was performed using Investigator ProGest Digestion Station (Genomic Solutions). The sample plate (96-well pink plate) was placed onto the reaction block. A white sample collection plate was placed onto the collection block. The method used, Ruby48proGestv1, was based on the software ProGest Method Editor (v.1.1.0.29). Then the samples were digested automatically with trypsin (0.19 µg/well) at 37 °C for overnight.

MALDI-TOF-MS Analysis

[0290] After in-gel digestion, the digest was concentrated and desalted by using C18 reversed phase Ziptip (Millipore, Bedford, MA). Bound peptides were eluted with 4 µL matrix solution (α-cyano-4-hydroxycinnamic acid in acetonitrile/0.1%TFA 1:1 v/v).

[0291] 1 µL eluted solution was spotted onto the MALDI target. Peptide mass mapping was performed on an ABI Voyager STR matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometer (Applied Biosystems, Framingham, MA). The acceleration voltage was 20 kv, the grid voltage was 14kv, the extraction delay time was 300nsecexternal calibration during mass spectrometry data acquisition was used. The acquired peptide mass mapping spectra was processed and analyzed by Data Explorer software (Version 4.0.0.0.). The internal calibration was performed by using trypsin autolysis peptide mass 842.5099 and 2211.1046.

MALDI-MS/MS Analysis

[0292] The MALDI-MS/MS analysis was performed using API Qstar Pulsar equipped with oMALDI Source (PE Sciex). The curtain gas was 25, the declustering potential was 45, the focusing potential was set from range 220 to 250 V various by samples. CAD gas was 7 and collision energy was at 35 to 100 depending on samples. The ion energy was set at 1 kV. Data acquisition and processing was done using Analyst QS and oMALDI Server (v. 2.2) softwares. The biomaker identification was obtained with MASCOT database search using MS/MS spectra. The publically accessible link to the “MASCOT” tool for protein identification using peptide data is:

<www.matrixscience.com/cgi/index.pl?page=/search_form_select.html>.

ELISA Analysis

[0293] Reagents for human pro-Matrix Metalloproteinase 1 (pro-MMP-1) ELISA kits were obtained from R& D Systems, Inc. (Minneapolis, MN; catalog # DMP100). ELISAs were performed on conditioned media samples according to the manufacturers' instructions. The optical density of each well was determined using a universal microplate spectrophotometer (μ Quant) from Bio-Tek Instruments, Inc. (Winooski, VT). KC-4 software from Bio-Tek Instruments, Inc. was used to extrapolate cytokine concentrations from the standard curves.

2. Additional studies using Compound 1 – Results

2D Gel Analysis of Conditioned Media from VEGF +/- Compound 1 Treated HUVECs.

[0294] Conditioned media isolated from HUVECs pre-treated with vehicle (DMSO) or Compound 1 (1uM) and subsequently stimulated with VEGF for 24 and 48 hours or baseline, untreated samples were analyzed by 2D gel analysis (see Materials and Methods). This analysis identified 1 spot (#1202) whose abundance consistently increased with addition of VEGF in two separate gel runs and appeared to decreased with Compound 1 pre-treatment, although not consistently using this technology (Table 15). These spots were excised and underwent MALDI and MALDI-MS/MS analysis for subsequent protein identification.

Identification of Interstitial Collagenase Precursor/pro-MMP1 By Database Search Based On Peptide Mass Fingerprint Spectra.

[0295] Peptide mass fingerprint data sets were analyzed by searching SwissProt protein database with ProteinProspector MS-Fit (Version 3.2.1). The searches were set with the following parameters, Human Mouse (Species), 1-66 kDa (molecular weight range), trypsin used for digest, maximum one missed cleavage, mass tolerance 50 ppm. Methionine was set as modified by oxidation and cysteine was set as modified by carbamidomethylation. Peptides were considered with hydrogen at N terminus and free acid at C terminus. The peptide masses were monoisotopic. The database search result was significant if the protein was ranked as the first hit and the sequence coverage was more than 30%, in addition a MOWSE score higher than 1e+003 (MS-Fit) was required. As summarized in Table 16 and

Table 17, Spot 1202 was definitively identified as interstitial collagenase precursor (pro-MMP1).

ELISA Analysis of pro-MMP1 Levels in HUVEC Conditioned Media

[0296] Because the quantitation of pro-MMP1 levels in 2D gels is only semi-quantitative (and therefore less consistent), the levels of pro-MMP-1 in HUVEC conditioned media were also assayed using a quantitative ELISA assay. The ELISA analysis indicated that levels of pro-MMP1 increase quantitatively when HUVEC cells are treated with VEGF and are decreased with pre-incubation of Compound 1 at 10nM, 100nM or 1uM concentrations (Table 18).

Pro-MMP1 Levels in Plasma from Compound 1 Treated Patients in Study B

[0297] Pro-MMP1 levels in the plasma of Study B patients after treatment with Compound 1 (day 1 pre-treatment, day 1 24 hr post-treatment, day 13 pre-treatment, day 13 12 hr post-treatment, and day 13 24 hr post-treatment) was analyzed. The results (see Table 19) demonstrate that pro-MMP1 levels increased in the plasma of patients after they received Compound 1.

J. EXAMPLES – MORE STUDIES USING COMPOUND 1

1. More studies using Compound 1 – Materials and Methods

Plasma Samples

[0298] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site.

[0299] Plasma samples were then thawed and centrifuged to remove particulate matter (10 min @ 5000 x g). The resulting supernatants were collected and split into aliquots and were re-frozen at -80 °C. Prior to assay, samples were thawed, Immunoglobulin Inhibiting Reagent (IIR, Bioreclamation Inc) was added to a final concentration 0.25 mg/mL, and Tween 20 was added to final concentration of 0.1%.

Antibody chip microarray manufacture

[0300] Glass slides were cleaned and derivatized with 3-cyanopropyltriethoxysilane. The slides were equipped with a Teflon mask, which divided the slide into sixteen 0.65 cm diameter wells or circular analysis sites called subarrays. Printing was accomplished with a Perkin-Elmer Spotarray Enterprise non-contact arrayer equipped with piezoelectric tips, which dispense a droplet (~350 pL) for each microarray spot. Antibodies were applied at a concentration of 0.5 mg/mL at defined positions. Each chip was printed with sixteen copies of one type of array, either Array 1.1 or Array 2.1 (see below). Both arrays consist of capture antibodies against different analytes and are defined by the antibody set contained. Analytes measured using both arrays are listed in Table 20.

Array 1.1 detector set.

Analyte	Name
ANG	Angiogenin
BLC (BCA-1)	B-lymphocyte chemoattractant
EGF	Epidermal growth factor
ENA-78	Epithelial cell-derived neutrophil-activating peptide
Eot	Eotaxin
Eot-2	Eotaxin-2
Fas	Fas (CD95)
FGF-7	Fibroblast growth factor-7
FGF-9	Fibroblast growth factor-9
GDNF	Glial cell line derived neurotrophic factor
GM-CSF	Granulocyte macrophage colony stimulating factor
IL-1ra	Interleukin 1 receptor antagonist
IL-2 sR α	Interleukin 2 soluble receptor alpha
IL-3	Interleukin 3
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-6	Interleukin 6
IL-7	Interleukin 7
IL-8	Interleukin 8
IL-13	Interleukin 13
IL-15	Interleukin 15
MCP-2	Monocyte chemotactic protein 2
MCP-3	Monocyte chemotactic protein 3
MIP-1 α	Macrophage inflammatory protein 1 alpha
MPIF	Myeloid progenitor inhibitory factor 1
OSM	Oncostatin M
PIGF	Placental growth factor

Array 2.1 detector set.

Analyte	Name

AR	Amphiregulin
BDNF	Brain-derived neurotrophic factor
FLT-3 Lig	fms-like tyrosine kinase-3 ligand
GCP-2	Granulocyte chemotactic protein 2
HCC4 (NCC4)	Hemofiltrate CC chemokine 4
I-309	I-309
IL-1 α	Interleukin 1 alpha
IL-1 β	Interleukin 1 beta
IL-2	Interleukin 2
IL-17	Interleukin 17
MCP-1	Monocyte chemotactic protein 1
M-CSF	Macrophage colony stimulating factor
MIG	Monokine induced by interferon gamma
MIP-1 β	Macrophage inflammatory protein 1 beta
MIP-1 γ	Macrophage inflammatory protein 1 delta
NT-3	Neurotrophin 3
NT-4	Neurotrophin 4
PARC	Pulmonary and activation-regulated chemokine
RANTES	Regulated upon activation, normal T expressed and presumably secreted
SCF	Stem cell factor
sgp130	Soluble glycoprotein 130
TARC	Thymus and activation regulated chemokine
TNF-RI	Tumor necrosis factor receptor I
TNF- α	Tumor necrosis factor alpha
TNF- β	Tumor necrosis factor beta
VEGF	Vascular endothelial growth factor

Microarray Chip Physical Quality Measures

[0301] Each print run of microarray chips was assigned a unique Production Sheet Number, and the RCAT immunoassay run for this print run was documented. For each print run, printed slides were subjected to the following control measures:

- (1) two slides, one from the start and one from the end of the run, were inspected

using light microscopy. If the percentage of missing spots observed was greater than 5%, then the batch failed and the slides were discarded immediately. For all print runs described herein, 100% of the printed spots were present on slides selected for this examination; and (2) for each print run, two of the printed slides were examined by a Cy5-labeled goat-anti-mouse antibody (GAM-Cy5). Since the majority of capture antibodies in these arrays were of mouse origin, this procedure examined total antibody attachment and provided a rapid measure of surface and binding uniformity. To account for differences in binding efficiency for different capture antibodies, the intensities of all spots for each individual capture antibody were measured across the chip (4 spots/subarray, 64 spots/chip) and a %CV was calculated for that feature. The average of these %CVs for all quantified capture antibodies must be below 20% for the print batch to pass. Chips treated with GAM-Cy5 were also checked for missing spots after the assay and if the percentage of missing spots was greater than 5%, then the batch failed (for these studies 100% of the printed spots were still present after this assay). Following these QC measures, qualified slides were stored at 4°C until used.

Reagent Quality Control Measures

[0302] The assay suite was considered as consisting of the microarray chips, detector antibodies and the reagents required for the RCAT portion of the assay. There were validation procedures for these reagents individually as well as a functional validation of the entire set. Reagents used in the RCA portion of the assay were from reserved vendor lots where possible. Materials produced in-house were subjected to QC procedures and qualified on microarray chips before release. If lot numbers changed for a particular reagent that is supplied by an outside vendor, the new lots were qualified by comparison with existing qualified stocks.

[0303] For each array type, a concentrated batch of detectors was prepared which consisted of a mixture of biotinylated antibodies directed against all analytes represented by an array. A functional QC was then performed for each detector antibody batch by carrying out the standard RCAT assay on a specially prepared sample set. Mixtures of 2-3 different cytokines were prepared so as to provide a high intensity signal and applied to 14 wells of a chip (with each well being treated with a different mixture up to the total complement of detector antibodies) and two arrays

were used as blank controls. The chips were developed and scanned and the resulting signals were compared to the positional map of the particular array. This examination demonstrated that the stock detector mixture was complete and the features were active. Once a detector batch had passed this QC, it was distributed into smaller volumes and released for use in the assay.

Positional and Functional Quality Measures

[0304] Following printing, a set of microarray chips was validated in concert with the qualified reagents discussed above. This was a two-part quality control measure. The first portion was identical to the detector antibody qualification procedure just described. In this case, the high intensity signals were compared to the array map and the proper positioning of capture antibody replicates was verified. The second test was a functional QC for all analytes of a specified array using known sample matrices. Normal human serum (Jackson ImmunoResearch Laboratories, Code#009-000-121) and heparinized plasma were assayed neat or spiked with purified recombinant cytokines representing all analytes in the array. Spiked mixtures were then titrated down the subarrays of a slide from 5,000 pg/ml to 20 pg/mL of spiked cytokine concentrations along with three subarrays for each un-spiked control sample. The data was quantified and for every analyte in the array a titration curve was generated to show that the feature intensity was above background and exhibiting increasing intensity with increasing analyte concentrations.

RCA Immunoassay

[0305] Prior to assay, the slides were removed from storage at room temperature in sealed containers and opened in a humidity controlled chamber (35-40%). Blocking was done by submerging the slides in a Coplin jar filled with blocking buffer (Seablock, Pierce Chemical Co., 1:1 dilution with 1X PBS) pre-chilled to 4°C, and placing the Coplin jar in a 37°C incubator for 1 hour. The slides were then washed twice (2 min per wash) in 60 mL of 1x PBS/0.5% Brj-35 washing buffer. On each slide, control serum (Jackson ImmunoResearch Laboratories) was applied to one subarray, plasma control applied to two subarrays, and a negative control with PBS buffer applied to two subarrays. The test samples were assayed on the remaining 11 subarrays. Twenty microliters of the treated sample were then

applied to each subarray. The basics of performing immunoassays with RCA signal amplification has been described (*Nat. Biotechol.* (2002) 20:359-65) and we are using SOPs derived from the protocols used in that study. Slides were scanned (GenePix 4000B, Axon Instruments Inc.) at 10 µm resolution with a laser setting of 100% and a PMT setting of 550 V. Mean pixel fluorescence values were quantified using the fixed circle method in GenePix Pro 4.0 (Axon Instruments). Using proprietary software, the fluorescence intensity of microarray spots was analyzed for each feature and sample, and the resulting mean intensity values were determined. Dose-response curves for selected cytokines were examined, ensuring that feature intensity is above background and exhibiting increasing intensity with increasing analyte concentration.

ELISA Analysis

[0306] Reagents for FLT3 ligand (FL) and IL-6 ELISA kits were obtained from R& D Systems, Inc. (Minneapolis, MN; catalog #s DFK00, Q6000). C-reactive protein (CRP) (accession ID AAA 52075) ELISA kits were obtained from KMI Diagnostics (Minneapolis, MN; catalog #EU59131). ELISAs were performed on patient plasma according to the manufacturers' instructions. The FL and CRP kits relied on a colorimetric readout; the optical density of each well was determined using a microplate spectrophotometer and data was analyzed using KC-4 software from Bio-Tek Instruments, Inc. The IL-6 kit was a chemiluminescent sandwich ELISA; luminescence values were determined on a microplate luminometer. SOFTmaxPRO software was used to extrapolate cytokine concentrations from the standard curves.

2. More studies using Compound 1 – Results

Plasma markers identified using Antibody chip technology

[0307] A multiplex antibody chip based approach (MSI, Molecular Staging Inc.) was used to identify plasma biomarkers of compound 1. Plasma samples harvested from 3 advanced malignancy patients pre and post Compound 1 treatment (Phase I trial A) were used for this analysis. Twenty three of 108 markers tested, showed changes following Compound 1 treatment (day 28). These are listed in Table 21. Controls included normal donor plasma which did not show significant changes

in these markers. Each of these is a potential biomarker of Compound 1, and may reflect drug exposure, biological activity or efficacy.

[0308] A number of markers showing the most dramatic changes and/or of known biological significance were further investigated (specifically VEGF, PLGF, IL-6, IL-8 and MCP-1). The relative changes were validated by ELISA on the same patient samples assessed in the antibody chip screen, and both methods showed good concordance (Table 22). Several of these markers had previously been identified by ELISA analysis on compound 1 treated samples, (PLGF, VEGF, IL-6), and several were novel (FLT3 ligand and MCP-1). Additional data on FLT3 ligand levels tested in an expanded set of patients is provided in Figure 25. Dramatic induction was observed following Compound 1 treatment in all cases.

Plasma ELISA Studies

[0309] In an effort to identify novel biomarkers of exposure to Compound 1, plasma samples were analyzed from 18 patients enrolled in Trial B. Plasma was taken both before study (D1 PRE) as well as at the end of the first cycle of treatment (Day 28 POST). Each time point was measured in triplicate and the standard deviation from the mean was calculated. Both the mean value and standard deviation for each patient at each time point is shown graphically in Figure 25. It was found that 100% of the patients exhibited an increase in FLT3 ligand (FL) concentration from day 1 to day 28. In 14 out of 18 patients, the increase was more than four-fold. The increase in FLT3 ligand concentration is attributed to treatment with Compound 1.

Plasma ELISA Studies – Fatigue Correlation

[0310] To find biomarkers that correlated with fatigue, plasma samples were analyzed from 62 patients enrolled in trials for Compound 1. Samples were taken before study (D1) and either two or four weeks after the start of cycle 1 dosing (Day 13 for trials B, C and D and Day 28 for A and E). The patients are grouped according to their highest recorded fatigue grade (0-4 scale from the NCI Common Toxicity Criteria). As seen in Figure 26, there is a statistically significant difference between the increases in IL-6 seen in patients with low fatigue (Grade 1 or 0) and those with

moderate to high fatigue (Grade 3 or 4), $p=0.001$. Thus, a patient who exhibits a large change in IL-6 plasma concentration (greater than two-fold) after treatment with Compound 1 has a much higher chance of experiencing a high degree of fatigue (Grade 3 or 4) than a patient whose IL-6 level remains more stable.

[0311] Plasma samples were further analyzed from 18 patients enrolled in Trial B for Compound 1. Samples were taken before study (D1) and two weeks after the start of cycle 1 dosing (D13). As shown with IL-6 levels, the patients are grouped according to their highest recorded fatigue grade (0-4). See Figure 27. It was determined there is a statistically significant difference in C-reactive protein (CRP) (accession ID AAA 52075) induction between patients with little fatigue (Grade 0, 1, or 2) and those with moderate to severe fatigue (Grade 3 or 4), $p = 0.0088$. Therefore, patients with a greater than two-fold increase in C-reactive protein after treatment with Compound 1 are more prone to experiencing high fatigue than those who have smaller fold changes in CRP.

Plasma ELISA Studies –Corrolation to biological response and/or clinical efficacy

[0312] Levels of C-reactive protein were measured as described above for the experiments involving CRP and fatigue. ELISAs were performed on plasma samples from patients before treatment (i.e., baseline values). The patients' samples and results were divided into two groups based upon observed clinical outcome. Patients with stable disease (SD pts) were defined as patients on study for over 6 months. Patients with progressive disease (PD pts) were defined as patients who had come off study due to disease progression or lack of efficacy in fewer than 6 months. This separation of patients demonstrated that patients with progressive disease had much higher baseline levels of CRP than those patients who were stable (median values of 63.8 $\mu\text{g}/\text{mL}$ vs. 6.5 $\mu\text{g}/\text{mL}$, respectively) (Figure 28). If a patient were to have a baseline level of CRP of above 20 $\mu\text{g}/\text{mL}$ before treatment, that patient has a greater chance of rapidly progressing than if the level of CRP were below 20 $\mu\text{g}/\text{mL}$. Thus, CRP is a baseline marker of biological response and/or clinical efficacy.

K. EXAMPLES – COMPOUND 1 STUDIES OF OB-CADHERIN 1 PROTEIN

1. Compound 1 studies of OB–cadherin 1 protein – Materials and Methods

Tumor samples

[0313] Colo205 human colon xenograft tumors were isolated and fixed in Streck Tissue Fixative (Streck Laboratories, Inc., La Vista, NE). Samples used in immunohistochemistry were sent out to BioPathology Sciences Medical Corporation (South San Francisco, CA) for paraffin embedding and sectioning.

Antibodies

[0314] A rabbit polyclonal antibody recognizing the cytoplasmic tail region of OB-cadherin 1 (cadherin 11) was purchased from Zymed Laboratories, Inc. (Zymed reagent #71-7600; South San Francisco, CA).

Immunohistochemistry

[0315] Sections (4-5 µm) stained using an automated immunohistochemistry system (Benchmark System, Ventana Medical Systems, Inc., Tucson, Arizona). In brief, slides were deparaffinized using heat at 75°C and Ventana's EZ Prep product (Ventana reagent #950-102). Antigen retrieval was performed by incubating the slides for 30 min with Ventana's CC2 product (Ventana reagent #950-123), a citrate-based solution with pH 6.0. Primary antibody (5 µg/ml) was incubated for 24 min at room temperature, followed by a secondary detection system, using biotinylated secondary antibody (Vector anti-rabbit secondary, BA-1000, at 2.5 µg/ml; Vector Laboratories, Burlingame, CA) with incubation time of 8 min. Streptavidin-horseradish peroxidase with 3, 3' diaminobenzidine as a substrate were used in conjunction with the secondary detection system. All samples analyzed for OB-cadherin 1 expression were also stained with the omission of primary antibody as a negative control.

2. Compound 1 studies of OB-cadherin 1 protein – Data Summary

[0316] As expression of OB-cadherin 1 (cadherin 11) RNA was found to be up-regulated at 24 hour post-Compound 1 treatment (see Table 12), effects on OB-cadherin 1 expression at the protein level was also examined. Colo205 xenograft tumors were isolated from Compound 1-treated mice at 24 and 48 hours post treatment. Tumors were fixed in formalin and sections were isolated and processed for immunohistochemistry (IHC).

[0317] Tissue sections were stained with an antibody that recognizes OB-cadherin 1. As a negative control, adjacent sections were processed similarly but with the omission of a primary antibody. This analysis identified up-regulation of OB-cadherin 1 protein in Colo205 tumors treated with Compound 1 for 24 and 48 hours as compared to vehicle treated samples (Figure 29).

TABLES**Table 1.**

	Number of samples from which RNA was processed	Number with RNA yield >1ug, at both d1 and d56	Number hybridized to U95A chips	Number for which data passed Quality Control inspection for further analysis
SU5416				
CR	0	0	0	0
PR	13	8	6	6*
MR	6	3	2	1
SD	6	5	1	1
PD	10	7	6	5*
Control				
CR	1	1	1	1*
PR	9	5	5	5*
MR	4	1	1	0
SD	3	2	2	2
PD	11	9	7	6*
Total:	63	41	31	27

* These samples were included in the dataset used in detailed analysis

Table 2.

<u>Affymetrix number</u>	<u>Gene name/ Symbol</u>	<u>Putative function(s)</u>	<u>Increased in SU5416 arm</u>	<u>Increased in Control arm</u>
34546_at	Defensin α 4	Corticostatic, Ca channel regulator	10 of 11	6 of 12
33530_at	CEA CAM 8	Tumor antigen, integral membrane protein.	9 of 11	4 of 12
37054_at	BPI	Anti-pathogen response	9 of 11	4 of 12
31859_at	MMP-9	Protease; ECM maintainence	8 of 11	2 of 12
32821_at	Lipocalin 2	Anti-pathogen response; apoptosis	10 of 11	5 of 12
34319_at	S100 P	Ca-binding protein	9 of 11	3 of 12
41249_at	Hypothetic. Protein FLJ13052	unknown	7 of 11	1 of 12
1962_at	Liver arginase	Amino acid metabolism	9 of 11	3 of 12
266_s_at	CD24 antigen	Anti-pathogen response; differentiation of B cells	9 of 11	0 of 12
31506_s_at	Defensin α 3	Chemotaxis; anti-microbial response	10 of 11	4 of 12
32275_at	Antileuko-protease	Secreted inhibitor of serine proteases	9 of 11	4 of 12
115_at	Thrombospondin 1	Blood clotting; angiogenesis	9 of 11	3 of 12
37149_s_at	Lactoferrin	Iron transport; putative protease	11 of 11	5 of 12

Table 3.

<u>Gene</u>	<u>Forward Primer</u>	<u>Reverse Primer</u>
Thrombospondin 1	TTGGCTACCAGTCCAGCAGC (SEQ ID NO: 1)	GGGTTGGTGTCCCAGTAGGA (SEQ ID NO: 2)
MMP-9	CCCGGAGTGAGTTGAACCA (SEQ ID NO: 3)	CCTAGTCCTCAGGGCACTGC (SEQ ID NO: 4)
Defensin α 3	CCCAGAAGTGGTTGTTCCCT (SEQ ID NO: 5)	GTCCATGTTTTCTTGAGCCT (SEQ ID NO: 6)
Lactoferrin	CTGGAAGCCTGTGAATTCC (SEQ ID NO: 7)	GAATGGCTAGGCTTCTTGG (SEQ ID NO: 8)
Lipocalin-2	GCTGACTTCGGAACAAAGGAGAA (SEQ ID NO: 9)	TGGGACAGGGAAGACGATGT (SEQ ID NO: 10)
CD24	CTGCCTCGACACACATAAACCTT (SEQ ID NO: 11)	CATCTAAGCATCAGTGTGACC A (SEQ ID NO: 12)

Table 4.

<u>P-value of Mann-Whitney U Test</u>		
<u>Gene</u>	<u>Affymetrix</u> (n = 23)	<u>SYBR Green RT-PCR</u> (n = 31)
MMP-9	0.0025	0.0748
Thrombospondin 1	0.0267	0.7186
CD24	0.0006	0.0057
Defensin α 3	0.0002	0.2196
Lactoferrin	0.0002	0.0065
Lipocalin-2 (LCN2)	0.0005	0.0057

Table 5.

Gene	n	Rank Sum (Treatment)	Rank Sum (Control)	Mann-Whitney U	p-value
MMP-9	36	415	251	0.0095	
CD24	36	443	223	0.0005	
Lactoferrin	36	460	206	0.0001	
LCN2	36	419	247	0.0065	

Table 6.

Predictor Gene Set for discriminating between the control and Compound B arms: LCN2, CD24, Lactoferrin

1. All cases pooled (67 cases from both trials)

	Control	Treatment	% Correct
Control	26	5	84
Treatment	6	30	83
Total	32	35	84

2. Jackknifed classification matrix for all cases pooled (67 cases from both trials)

	Control	Treatment	% Correct
Control	26	5	84
Treatment	8	28	78
Total	34	33	81

3. Prediction subset (randomly selected 34 cases) from all cases pooled (67 cases in both trials)

	Control	Treatment	% Correct
Control	13	1	93
Treatment	4	16	80
Total	17	17	85

4. Validation subset (randomly selected 33 cases) from all cases pooled (67 cases in both trials)

	Control	Treatment	% Correct
Control	11	6	65
Treatment	5	11	69
Total	16	17	67

Table 7.**Trial C patients 1-23 PLGF plasma level ratios**

Patient #	d1 (6 hr):d1 (0 hr)	d29:d1	d42:d1	
1	0.695512	1.871238	0.398897	
2	2.050289	11.96579	1.040025	
3	1.965517	3.586207	1.206897	
4	1.985061	24.72922	1.985061	
5	1.09557	11.3316	1.09557	
6	1.800672	11.02117	1.365586	
8	1.16493	12.38985	1.157115	
10	1.622462	>10	2.652309	
11	1.250022	7.511615	1.386382	
13	1.038442	1.817441	NA	***Note: d15:D1 ratio is 6.4 for pt. 13
15	0.896403	6.651554	1.189041	
17	0.907692	19.21308	1.134385	
18	1.007357	12.30822	1.105295	
20	1.2261	11.29078	1.598445	
21	1.518564	14.84205	0.955559	
22	1	2.423462	0.815385	
Average	1.326537	10.19689	1.272397	

Table 8.

<u>MIG</u>					<u>IP-10</u>		
<u>Patient</u>	<u>day 1</u>	<u>day 15</u>	<u>end C1 dosing</u>	<u>Ratio</u>	<u>day1</u>	<u>end C1 dosing</u>	<u>Ratio</u>
11 (B)	41.927		739.71	17.64281	55.617	>500	>9
1	48.375		1066.2	22.04031	64.847	>500	>7.7
11	34.432		344.93	10.01772	65.32	384.06	5.879669
17	166.8		907.09	5.438189	72.29	>500	>6.9
24	80.751		314.2	3.890973			
26	80.751		995.47	12.32765	64.296	>500	>7.7
27	80.826		81.439	1.007584			
7	106.04		145.64	1.373444	139.2	240.31	1.726365
20	161.91		698.23	4.312458	73.67	>500	>6.9
22	37.685	339.16		8.999867			
9 (A)	60.393		138.56	2.294306			

I-TAC

<u>Patient</u>	<u>day 1</u>	<u>day 15</u>	<u>end C1 dosing</u>	<u>Ratio</u>
11 (B)	428.83		>4000.0	>9
1				
11				
17				
24	259.38		771.04	2.972627
26	97.917		701.46	7.163822
27	139.94		315.69	2.255895
7				
20				
22	190.76	2020.2		10.59027
9 (A)	59.975		212.26	3.539141

Table 9.

<u>Patient #</u>	<u>PLGF Ratio (end dosing:d1)</u>	<u>VEGFR2 ratio (end dosing:d1)</u>	<u>Primary Diagnosis</u>
Trial C			
1	1.871237941	0.265856292	Synovial Sarcoma
2	11.96579454	0.25171334	Rectal
3	3.586206897	0.5673112	Gall-bladder
4	24.72921991	0.34236691	Hepatocellular
5	11.33159926	0.406890612	Melanoma
6	11.02116835	0.572980623	Breast
7	23.86685363	0.404286499	Ovary
8	12.38984817	0.318366334	Small Cell Lung
10	10	0.45614753	Melanoma
11	7.511615487	0.323681006	Met. Colon
13	1.817440506	0.460416464	Renal Cell Carcinoma
14	3.080408542	0.575703582	Met. Melanoma
15	6.651553529	0.506347193	Renal Cell Carcinoma
17	19.21307692	0.177452364	NSCLC
18	12.30822285	0.271285002	NSCLC
20	11.29078149	0.385479698	Colon
21	14.84205128	0.369637606	Breast
22	2.423461538	0.479139734	Sarcoma
23	1	0.504789782	Sarcoma
24	0.99016936	0.457140878	met. Rectal carcinoma
25	12.03862173	0.250133543	Retropero Sarcoma
26	13.29469461	0.493391074	Met Pelvis Sarcoma
29	5.237072177	0.59927457	SCCR R) Parotid
30		0.519969363	Colon AdenoCA
31		0.330647033	Lung AdenoCA
Trial A			
1		0.565173104	Renal Cell Carcinoma
3		0.597994214	Bronchial adeno.
4		0.685465839	breast carcinoma
5	12.97391648	0.182557005	uterine
6	25.082632	0.458079657	pelvic angiosarcoma
7		0.648790016	pleural mesothelioma
8		0.64392508	uterine
9		0.38520981	Bronchial adeno.
10	5.301660143	0.44915001	colorectal
13		0.297438475	neuroendocrine

Table 9. cont.

Patient #	<u>PLGF Ratio (end dosing:d1)</u>	<u>VEGFR2 ratio (end dosing:d1)</u>	<u>Primary Diagnosis</u>
Trial D			
1		0.502083475	GIST
3	2.98130415	0.670742516	GIST
4	5.228142589	0.972905837	GIST
5	1.351061278	0.616277438	GIST
6	7.055260831	0.684932856	GIST
13	4.095209935	0.600072917	GIST
14	4.786806356	0.685754939	GIST
15	22.29951691	0.767346939	GIST
16	3.034877351	0.727153597	GIST
18	16.89889246	0.471077781	GIST
19	2.782095462	0.542935245	GIST
20	12.47129736	0.598602839	GIST
21	11.56450225	0.351218422	GIST
22	2.996492067	0.644054653	GIST
Trial B			
4		0.67109839	Head & Neck
5		0.678411145	CRC
6		0.4130696	thymic
7		0.301532905	CRC
8		0.456886687	thyroid
9		0.597322954	thyroid

Table 10.**MIG**

Patient #	day 1	day 15	end C1 dosing	Ratio	Cancer Type
11 (B)	41.927		739.71	17.64281	Pancreatic
1	48.375		1066.2	22.04031	Synovial Sarcoma
11	34.432		344.93	10.01772	Met. Colon
17	166.8		907.09	5.438189	NSCLC
24	80.751		314.2	3.890973	Met. Rectal
26	80.751		995.47	12.32765	Pelvis Sarcoma
20	161.91		698.23	4.312458	Colon
22	37.685	339.16		8.999867	Sarcoma
9 (A)	60.393		138.56	2.294306	Bronchial Adeno.

Table 11A.

Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Increase
Basic transcription factor 3 homologue	Transcription factor	M90354	6	2.1
c-jun proto oncogene	Transcription factor	J04111	6	2.5
c-fos cellular oncogene	Transcription factor	K00650	6	4.2
Tyrosine phosphatase non-receptor type 2	Protein phosphatase	NM_080422	6	2.2
cdc2-related protein kinase	Cell cycle regulation	M68520	6	19
Cyclin C	Cell cycle regulation	M74091	6	2.5
DNA polymerase gamma	DNA polymerase	U60325	6	7.3
Basic transcription factor 3 homologue	Transcription factor	M90354	24	2.2
Protein kinase C alpha	Protein kinase	X52479	24	3.0
Lipocortin II/annexin A2	Ca ⁺⁺ -regulated membrane binding protein	D00017	24	2.3
Histone H2B, member R	Transcriptional regulation	AF531293	24	3.0
Amphiregulin	Growth factor	NM_001657	24	6.1

Table 11A cont.

Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Decrease
Ephrin receptor EphB4	Tyrosine kinase receptor	NM_004444	6	2.5
Hanukah factor/Granzyme A	Serine protease	M18737	24	2.3
von Hippel-Lindau (VHL) tumor suppressor	Tumor suppressor	NM_000551	24	3.7
OB-cadherin 1	Ca ⁺⁺ -dependent cell adhesion protein	D21254	24	2.2
OB-cadherin 2	Ca ⁺⁺ -dependent cell adhesion protein	D21255	24	2.0
Phosphoinositol 3-phosphate-binding protein-3 (PEPP3)	Phosphoinositide-binding protein	NM_014935	24	2.1
Phosphoinositol 3-Kinase, p85 subunit	Proliferation	M61906	24	2.2
Mucin 1	Adhesion, cell-cell interaction	J05582	24	2.5
Hepatitis C-associated microtubular aggregate p44	Interferon-induced protein	Exon 1-9 D28908, D28909, D28910, D28911, D28912, D28913, D28914, D28915	24	2.0
ErbB3/HER3 receptor tyrosine kinase	Growth factor receptor	M29366	24	2.1

Table 11B.

Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Increase
Vinculin	Cell adhesion	M33308	4	2.5
Basic transcription factor 3	Transcription factor	M90357	24	2.2
Phosphoinositol 3-kinase, p110 subunit	Proliferation	NM_006219	24	4.5
Transcript Name	Putative Role	Accession No.	Time Point (hrs)	Fold Change Decrease
Gelsolin	Actin binding protein	X04412	4	2.1
Cyclin D2	Transcription	NM_001759	4	2.2

Table 12.

Transcript Name	Accession No.	Relative Expression Level (6 hr)	Relative Expression Level (24 hr)
Amphiregulin	NM_001657	1.9	2.5
Cdc2-related protein kinase	M68520	0.43	0.55
Phosphoinositol 3-kinase, p110 subunit	NM_006219	0.59	1.6
Cyclin C	M74091	842	22.3
OB-cadherin 1	D21254	0.35	23.8
OB-cadherin 2	D21255	0.40	0.51
Phosphoinositol 3-kinase, p85 subunit	M61906	1.0	2.30
Mucin 1	J05582	0.32	1.13
von Hippel-Lindau tumor suppressor	NM_000551	0.9	0.55
Ephrin receptor, EphB4	NM_004444	3.5	31
Gelsolin	X04412	4.0	0.04

Table 13.

Transcripts	GenBank Accession No.	Forward Primer (5' - 3')	Reverse Primer (5' - 3')	Taqman Probe (5' - 3')
Amphiregulin	NM_001657	ATGATGAGTCCGGTCCCT TTCC (SEQ ID NO: 13)	TGACAATTGAAAGTTAA AACCATCATA (SEQ ID NO: 14)	TCCATTGTCTTATGA TCCAC (SEQ ID NO: 15)
CDK-2 related protein	M68520	AGTTAGAAGTTAGGGTT AGGCATCATT (SEQ ID NO: 16)	TACCCATGCCCTCACTCA ATC (SEQ ID NO: 17)	AAGTGTCAAGCATTC CAA (SEQ ID NO: 18)
PI3-kinase, p85 p110	NM_006219	CCAGTGTGAGGATGC ATATC (SEQ ID NO: 19)	CAGTCAACATCAGCGCAA AGA (SEQ ID NO: 20)	ATTCCCCATGCCGTCG TA (SEQ ID NO: 21)
PI3-kinase, p85	M61906	CAAACCTACTGTATCTCT AATACAGTGTGACT (SEQ ID NO: 22)	GACAGAGATGATTATCCC TTAAACCA (SEQ ID NO: 23)	AGGGCTCACCTTTG (SEQ ID NO: 24)
Cyclin C	M74091	CCTACAGACAGACATACA TAGACATTCAA (SEQ ID NO: 25)	ATTATGCTTCATGTTTCCT GGCTTA (SEQ ID NO: 26)	CCAATAAAGAAAT ATTATACTAACATCA (SEQ ID NO: 27)
OB-cadherin 1	D21254	GACAACAGTTCTGAGCTG TAATTTCG (SEQ ID NO: 28)	TGGGTTAACGCTGGCTGA ATATTAT (SEQ ID NO: 29)	ACTCTGGACACTCTA TATGT (SEQ ID NO: 30)
OB-cadherin 2	D21255	TCAGGCCAGCTTAAACCA TACAA (SEQ ID NO: 31)	TGGCACGTTAGGTTAA GATGAAAAGTAG (SEQ ID NO: 32)	CTTGGTTACTGCTGAT TCT (SEQ ID NO: 33)
Mucin 1	J05582	TTCAGAGGGCCCCAACAT T (SEQ ID NO: 34)	CCACATGAGCTTCCACACA CA (SEQ ID NO: 35)	TCTCGGACACCTCTC (SEQ ID NO: 36)

Table 13 cont.

Transcripts	GenBank Accession No.	Forward Primer (5' - 3')	Reverse Primer (5' - 3')	Taqman Probe (5' - 3')
VHL tumor suppressor	NM_000551	TGAGGCAGGGACAAGTCT TTCT (SEQ ID NO: 37)	ACCCCTGACTGAAGGGCTCA TGA (SEQ ID NO: 38)	CTCTTGAGACCCCA GTGC (SEQ ID NO: 39)
EphB4	NM_004444	TCTACCGTCCTGTCAATA ACTTTGTG (SEQ ID NO: 40)	ATGATGATGGGCCCTGT T (SEQ ID NO: 41)	CCTTTGCCCAAAGTTG (SEQ ID NO: 42)
Gelsolin	X04412	TGGACCGTTTGTGATCGA AGAG (SEQ ID NO: 43)	AAGTCAAGGGCTTCTGTCT TTCTTCT (SEQ ID NO: 44)	CTTGAGAAATCCTTTC CAACC (SEQ ID NO: 45)

Table 14.

Gel No. 1	VEGF + DMSO - 48hr
Gel No. 2	Compound 1 + VEGF + DMSO - 48hr
Gel No. 3	VEGF + DMSO - 48hr

Table 15.

Spot #1202	Run #1	Run #2
Sample		
baseline	126	22.5
VEGF at 24h	437	192.4
VEGF at 48h	812	540
VEGF and compound 1 (1uM) at 24h	270	484.7
VEGF and compound 1 (1uM) at 48h	869	158

Table 16.

<u>SSP</u>	<u>Well</u>	<u>MALDI Mass Mapping result</u>	<u>MS-Fit</u>	<u>MOWSE Score</u>	<u>Sequence Coverage</u>
1202	A6	Interstitial Collagenase Precursor		3.64E+07	31%

Table 17.

<u>SSP</u>	<u>Well</u>	<u>Confirmed Peptide</u>	<u>File Name</u>	<u>MS/MS result</u>	<u>MASCOT Score</u>
1202	A6	DIYSSFGFPR (SEQ ID NO: 46)	spotA6-1188.wiff	MM01_HUMAN, Interstitial Collagenase Precursor P03956 53973/6.4	34
1202	A6	DGFFYFFHGTR (SEQ ID NO: 47)	spotA6prod1393-2.wiff	MM01_HUMAN, Interstitial Collagenase Precursor P03956 53973/6.4	22

Table 18.

HUVEC SAMPLE ¹	Average pro-MMP1 (ng/ml)	Standard Deviation
VEGF 10 min	4.66	0.3079
DMSO 10 min	4.64	0.1003
compound 1@ 10 nM 10 min	5.41	0.1224
Compound 1 @ 100 nM 10 min	5.78	0.3158
Compound 1 @ 1 uM 10 min	5.04	0.331
VEGF 8 hr	16.47	1.0048
DMSO 8 hr	17.63	1.2563
Compound 1 @ 10 nM 8 hr	14.93	1.1245
Compound 1 @ 100 nM 8 hr	12.75	0.6686
Compound 1 @ 1 uM 8 hr	14.48	1.0551
VEGF 24 hr	45.71	3.06
DMSO 24 hr	79.94	4.50
Compound 1 @ 10 nM 24 hr	70.21	4.82
Compound 1 @ 100 nM 24 hr	50.26	1.24
Compound 1 @ 1 uM 24 hr	50.42	2.42
VEGF 48 hr	244.74	3.91
DMSO 48 hr	234.72	10.85
Compound 1 @ 10 nM 48 hr	135.35	1.04
Compound 1 @ 100 nM 48 hr	128.75	11.05
Compound 1 @ 1 uM 48 hr	103.09	3.60

¹Time points indicated (10 min, 8h, 24h, 48h) refer to the period of time post-VEGF treatment after which samples were isolated.

Table 19.

	Pro-MMP1 (ng/ml)	FC vs d1 Pre¹	% Change vs d1 Pre
Pt 3 d1 Pre²	0.3115		
d1 24 hr	0.2837	-1.097990835	-8.924558587
d13 Pre	0.6756	2.168860353	116.8860353
d13 12 hr	0.6235	2.001605136	100.1605136
d13 24 hr	0.4035	1.295345104	29.53451043
Pt 4 d1 Pre	0.5214		
d1 24 hr	0.8938	2.869341894	71.42309168
d13 Pre	0.6246	2.005136437	19.79286536
d13 12 hr	0.4579	1.469983949	-12.17874952
d13 24 hr	0.4514	1.449117175	-13.42539317
Pt 5 d1 Pre	0.5739		
d1 24 hr	0.323	1.036918138	-43.71841784
d13 Pre	0.7269	2.333547352	26.65969681
d13 12 hr	0.6874	2.206741573	19.77696463
d13 24 hr	0.4171	1.339004815	-27.32183307
Pt 6 d1 Pre	0.2969		
d1 24 hr	0.6818	2.188764045	129.6396093
d13 Pre	0.7597	2.438844302	155.8773998
d13 12 hr	0.7992	2.56565008	169.1815426
d13 24 hr	1.066	3.422150883	259.043449
Pt 7 d1 Pre	0.5743		
d1 24 hr	0.7334	2.354414125	27.70329096
d13 Pre	0.7374	2.367255217	28.39979105
d13 12 hr	0.5154	1.654574639	-10.25596378
d13 24 hr	0.7203	2.312359551	25.42225318
Pt 8 d1 Pre	0.2879		
d1 24 hr	0.3664	1.176243981	27.26641195
d13 Pre	1.7166	5.510754414	496.2486975
d13 12 hr	1.1071	3.554093098	284.5432442
d13 24 hr	0.8494	2.726805778	195.0329976
Pt 9 d1 Pre	0.7786		
d1 24 hr	0.4816	1.546067416	-38.14538916
d13 Pre	0.4931	1.582985554	-36.66837914
d13 12 hr	1.047	3.361155698	34.47212946
d13 24 hr	2.6022	8.353772071	234.2152582
Pt 10 d1 Pre	0.3613		
d1 24 hr	0.2396	-1.300083472	-33.68391918
d13 Pre	1.2937	4.153130016	258.0680875
d13 12 hr	1.4224	4.566292135	293.6894547
d13 24 hr	1.0684	3.429855538	195.7099363

Table 19 cont.

Pt 11 d1 Pre	0.299		
d1 24 hr	0.2866	-1.08688067	-4.147157191
d13 Pre	0.6931	2.225040128	131.8060201
d13 12 hr	0.4496	1.443338684	50.36789298
d13 24 hr	1.1685	3.751203852	290.8026756
Pt 12 d1 Pre	0.8587		
d1 24 hr	0.5418	1.739325843	-36.90462327
d13 Pre	2.1689	6.962760835	152.5794806
d13 12 hr	2.1494	6.900160514	150.308606
d13 24 hr	5.9226	19.01316212	589.7170141

¹ Fold change of pro-MMP1 levels are indicated by “FC vs d1 pre”. These levels were calculated by dividing the levels of pro-MMP1 after drug treatment by the MMP1 levels present before drug treatment (d1 pre).

² Patient number is indicated (Pt), time point of sampling is indicated pre-treatment (d1 pre), 24 hours post first treatment (d1 24h), after 13 days of treatment (d13 pre), after 13 days and 12 hours post-treatment (d13 12h), and 13 days and 24hours of treatment (d13 24h).

Table 20.

5000 ng/mL Bio-mlgG	4000 ng/mL Bio-mlgG	BLANK	AR	BDNF	FGF-6	Fit3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mlgG	3000 ng/mL Bio-mlgG	2000 ng/mL Bio-mlgG
5000 ng/mL Bio-mlgG	4000 ng/mL Bio-mlgG	BLANK	AR	BDNF	FGF-6	Fit3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mlgG	3000 ng/mL Bio-mlgG	2000 ng/mL Bio-mlgG
5000 ng/mL Bio-mlgG	4000 ng/mL Bio-mlgG	BLANK	AR	BDNF	FGF-6	Fit3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mlgG	3000 ng/mL Bio-mlgG	2000 ng/mL Bio-mlgG
5000 ng/mL Bio-mlgG	4000 ng/mL Bio-mlgG	BLANK	AR	BDNF	FGF-6	Fit3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mlgG	3000 ng/mL Bio-mlgG	2000 ng/mL Bio-mlgG
5000 ng/mL Bio-mlgG	4000 ng/mL Bio-mlgG	BLANK	AR	BDNF	FGF-6	Fit3Lig	G-CSF	HCC4	I-309	IL-1α	IL-1β	IL-1sR1	0 ng/mL Bio-mlgG	3000 ng/mL Bio-mlgG	2000 ng/mL Bio-mlgG
1000 ng/mL Bio-mlgG	800 ng/mL Bio-mlgG	600 ng/mL Bio-mlgG	400 ng/mL Bio-mlgG	300 ng/mL Bio-mlgG	200 ng/mL Bio-mlgG	100 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	60 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	40 ng/mL Bio-mlgG	30 ng/mL Bio-mlgG	20 ng/mL Bio-mlgG	10 ng/mL Bio-mlgG	5 ng/mL Bio-mlgG	Blank
1000 ng/mL Bio-mlgG	800 ng/mL Bio-mlgG	600 ng/mL Bio-mlgG	400 ng/mL Bio-mlgG	300 ng/mL Bio-mlgG	200 ng/mL Bio-mlgG	100 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	60 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	40 ng/mL Bio-mlgG	30 ng/mL Bio-mlgG	20 ng/mL Bio-mlgG	10 ng/mL Bio-mlgG	5 ng/mL Bio-mlgG	Blank
1000 ng/mL Bio-mlgG	800 ng/mL Bio-mlgG	600 ng/mL Bio-mlgG	400 ng/mL Bio-mlgG	300 ng/mL Bio-mlgG	200 ng/mL Bio-mlgG	100 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	60 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	40 ng/mL Bio-mlgG	30 ng/mL Bio-mlgG	20 ng/mL Bio-mlgG	10 ng/mL Bio-mlgG	5 ng/mL Bio-mlgG	Blank
1000 ng/mL Bio-mlgG	800 ng/mL Bio-mlgG	600 ng/mL Bio-mlgG	400 ng/mL Bio-mlgG	300 ng/mL Bio-mlgG	200 ng/mL Bio-mlgG	100 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	60 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	40 ng/mL Bio-mlgG	30 ng/mL Bio-mlgG	20 ng/mL Bio-mlgG	10 ng/mL Bio-mlgG	5 ng/mL Bio-mlgG	Blank
1000 ng/mL Bio-mlgG	800 ng/mL Bio-mlgG	600 ng/mL Bio-mlgG	400 ng/mL Bio-mlgG	300 ng/mL Bio-mlgG	200 ng/mL Bio-mlgG	100 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	60 ng/mL Bio-mlgG	50 ng/mL Bio-mlgG	40 ng/mL Bio-mlgG	30 ng/mL Bio-mlgG	20 ng/mL Bio-mlgG	10 ng/mL Bio-mlgG	5 ng/mL Bio-mlgG	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
GCP-2	NT3	NT4	PARC	Rantes	SCF	SDF-1α	sgp130	TARC	TGF-β1	TNF-α	TNF-β	TNF-R1	TNF-RII	VEGF	Blank
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-15	NAP-2
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-15	NAP-2
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-15	NAP-2
Blank	IL-2	IL-6sR	IL-11	IL-12 p70	IL-16	IL-17	IP-10	LIF	MCP-1	M-CSF	MDC	MIG	MIP-1β	MIP-15	NAP-2

Table 21.

Patient	1, 2, 3	Patient	1, 2, 3
• ENA-78	(-) ↓ ↓	TNFR1	↑ ↑ (-)
• MPIF-1	(-) (-) ↓	VEGF	↑ ↑ (-)
• GCP-2	↑ (-) (-)	Flt3L	↑ ↑ ↑
• Amphireg	↑ (-) (-)	PLGF	↑ ↑ (-)
• IL-1 α	↑ ↑ (-)	IL6	↑ ↑ (-)
• IL-1 β	↑ ↑ (-)	MCP-1	↑ ↑ (-)
• IL-2	↑ ↑ (-)	TNF α	↑ ↑ (-)
• MIG	(-) ↓ (-)	TARC	↑ (-) (-)
• NT4	↑ (-) ↑	MMP7	↑ ↑ ↓
• GCP-2	↑ ↑ (-)	MMP9	(-) (-) ↑
• IGFBP-1	↑ ↑ ↑	leptin	(-) ↑ (-)
• GRO- β	↑ (-) ↑		

Table 22.

	Patient 1		Patient 2		Patient 3	
	ELISA	Ab Chip	ELISA	Ab Chip	ELISA	Ab Chip
VEGF	32	2.7	72	4.3	3	1.8
PLGF	13	4.6	25.1	21.7	5.3	1.6
IL-6	29	2.9	11.6	3.7	0.9	0.99
IL-8	2	1.5	2.7	1.8	0.77	1.7
FLT3 L	10.3	13.9	6.7	7.7	2.6	6.2
MCP-1	2.2	2.5	1.93	2	1.0	1.4

We claim:

1. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFa, TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

2. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPs core protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

3. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFa, TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

4. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-

cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

5. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPs core protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-

binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

- (b), exposing the mammal to the compound; and
- (c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal is responding to the compound that inhibits tyrosine kinase activity.

6. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

- (a) exposing the mammal to the compound; and
- (b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo

sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

7. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNFa, TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb

gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

8. A method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic

transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in the same type of mammal without cancer, the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

9. The method of any one of claims 1-8, wherein the mammal is a human, rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate or monkey.

10. The method of any one of claims 1-8, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one mammalian biological tissue from the mammal.

11. The method of claim 10, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

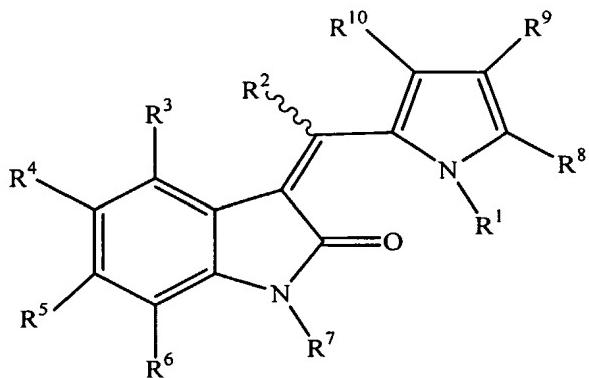
12. The method of claim 10, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

13. The method of any one of claims 1-8, wherein the mammal has cancer.

14. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is an indolinone compound.

15. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is:

a pyrrole substituted 2-indolinone having the formula:



wherein:

R¹, R² and R⁷ are hydrogen;

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

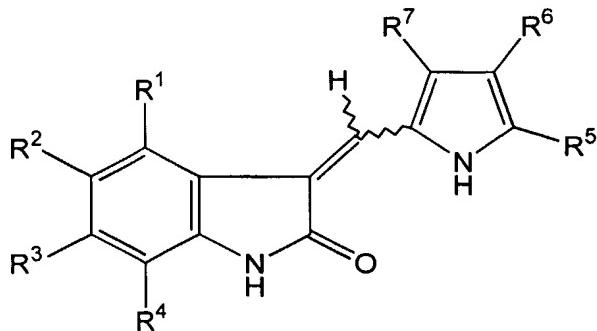
R⁸ is unsubstituted lower alkyl;

R⁹ is -(CH₂)(CH₂)C(=O)OH; and

R¹⁰ is unsubstituted lower alkyl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, $-(CH_2)_tR^{16}$ and $-C(O)NR^8R^9$;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-C(O)R^{15}$, aryl, heteroaryl, and $-S(O)_2NR^{13}R^{14}$;

R^3 is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy, $-(CO)R^{15}$, $-NR^{13}R^{14}$, aryl, heteroaryl, $-NR^{13}S(O)_2R^{14}$, $-S(O)_2NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-NR^{13}C(O)OR^{14}$ and $-SO_2R^{20}$ (wherein R^{20} is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R^4 is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and $-NR^{13}R^{14}$;

R^5 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^6 is selected from the group consisting of hydrogen, alkyl and $-C(O)R^{10}$;

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $-C(O)R^{17}$ and $-C(O)R^{10}$; or

R^6 and R^7 may combine to form a group selected from the group consisting of $-(CH_2)_4-$, $-(CH_2)_5-$ and $-(CH_2)_6-$;

with the proviso that at least one of R^5 , R^6 or R^7 must be $-C(O)R^{10}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl and aryl;

R^{10} is selected from the group consisting of hydroxy, alkoxy, aryloxy, $-N(R^{11})(CH_2)_nR^{12}$, and $-NR^{13}R^{14}$;

R^{11} is selected from the group consisting of hydrogen and alkyl;

R^{12} is selected from the group consisting of $-NR^{13}R^{14}$, hydroxy, $-C(O)R^{15}$, aryl, heteroaryl, $-N^+(O^-)R^{13}R^{14}$, $-N(OH)R^{13}$, and $-NHC(O)R^a$ (wherein R^a is unsubstituted alkyl, haloalkyl, or aralkyl);

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^{13} and R^{14} may combine to form a heterocyclo group;

R^{15} is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

R^{16} is selected from the group consisting of hydroxy, $-C(O)R^{15}$, $-NR^{13}R^{14}$ and $-C(O)NR^{13}R^{14}$;

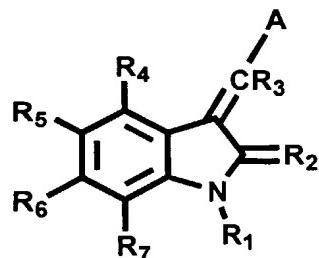
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

R^{20} is alkyl, aryl, aralkyl or heteroaryl; and

n and r are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R_1 is H;

R_2 is O or S;

R_3 is hydrogen;

R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-

oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R or CONRR';

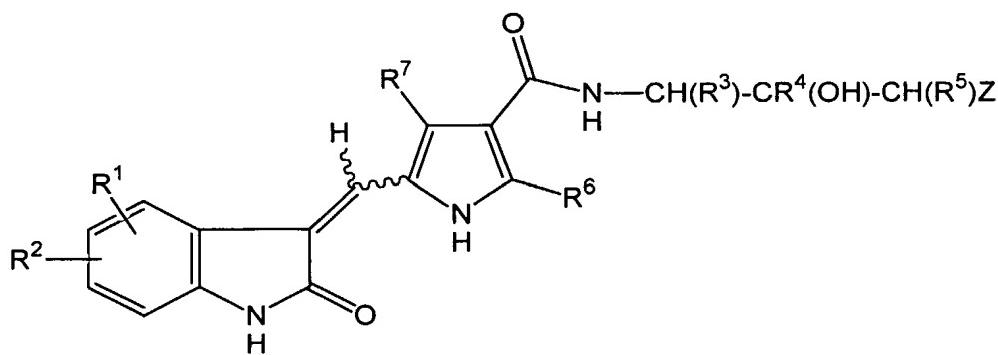
n is 0-3;

R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R¹ is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy, -C(O)R⁸, -NR⁹R¹⁰ and -C(O)NR¹²R¹³;

R² is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, -NR⁹R¹⁰, -NR⁹C(O)R¹⁰, -C(O)R⁸, -S(O)₂NR⁹R¹⁰ and -SO₂R¹⁴ (wherein R¹⁴ is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R³, R⁴ and R⁵ are independently hydrogen or alkyl;

Z is aryl, heteroaryl, heterocycle, or -NR¹⁵R¹⁶ wherein R¹⁵ and R¹⁶ are independently hydrogen or alkyl; or R¹⁵ and R¹⁶ together with the nitrogen atom to which they are attached from a heterocycloamino group;

R⁶ is selected from the group consisting of hydrogen or alkyl;

R⁷ is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and -C(O)R¹⁷ as defined below;

R⁸ is selected from the group consisting of hydroxy, alkoxy and aryloxy;

R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

R^9 and R^{10} combine to form a heterocycloamino group;

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a heterocycloamino;

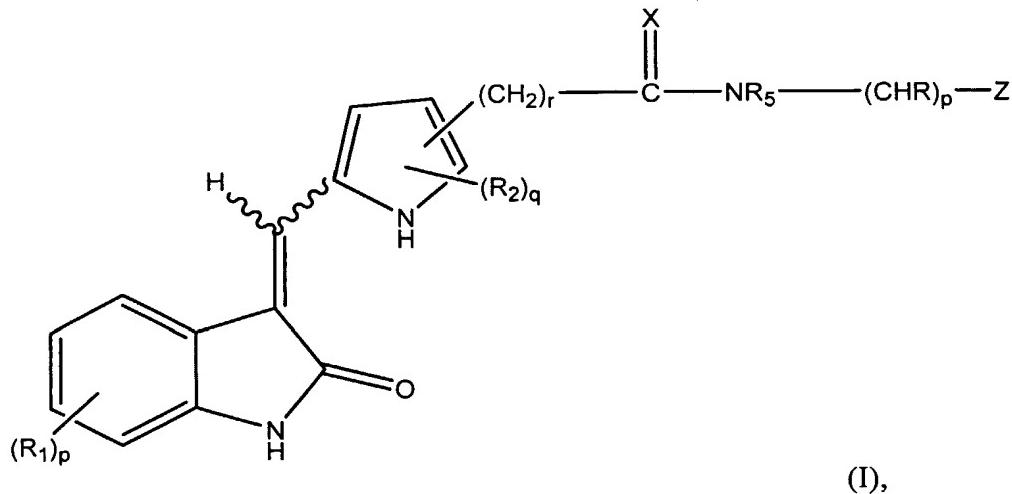
R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

16. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (Compound A) or a pharmaceutically acceptable salt thereof.

17. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one (Compound B) or a pharmaceutically acceptable salt thereof.

18. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula I:



wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R₁ is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈, -NR₉R₁₀, -NR₉C(O)-R₁₂ and -C(O)NR₉R₁₀;

each R₂ is independently selected from the group consisting of alkyl, aryl, heteroaryl, -C(O)-R₈, and SO₂R'', where R'' is alkyl, aryl, heteroaryl, NR₉N₁₀ or alkoxy;

each R₅ is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈ and (CHR)_rR₁₁;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

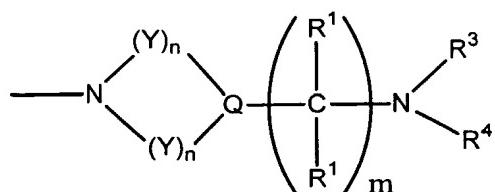
R₈ is selected from the group consisting of -OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R₉ and R₁₀ are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R₉ and R₁₀ together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R₁₁ is selected from the group consisting of -OH, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R₁₂ is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or -NR₃R₄, where R₃ and R₄ are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R₃ and R₄ may combine with N to form a ring where the ring atoms are selected from the group consisting of CH₂, N, O and S or

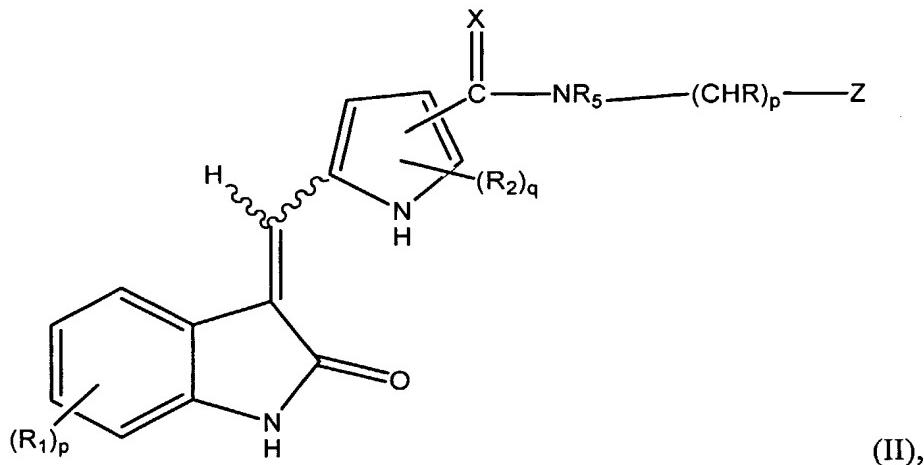


wherein Y is independently CH₂, O, N or S,

Q is C or N;

n is independently 0-4; and
 m is 0-3;
 or a pharmaceutically acceptable salt thereof.

19. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula II:



wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each R₁ is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈, -NR₉R₁₀, -NR₉C(O)-R₁₂ and -C(O)NR₉R₁₀;

each R₂ is independently selected from the group consisting of alkyl, aryl, heteroaryl, -C(O)-R₈, and SO₂R'', where R'' is alkyl, aryl, heteroaryl, NR₉N₁₀ or alkoxy;

each R₅ is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy, -C(O)-R₈ and (CHR)_rR₁₁;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

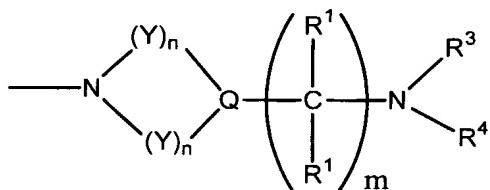
R₈ is selected from the group consisting of -OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or R_9 and R_{10} together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

R_{11} is selected from the group consisting of -OH, amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

R_{12} is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or $-NR_3R_4$, where R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or R_3 and R_4 may combine with N to form a ring where the ring atoms are selected from the group consisting of CH_2 , N, O and S or



wherein Y is independently CH_2 , O, N or S,

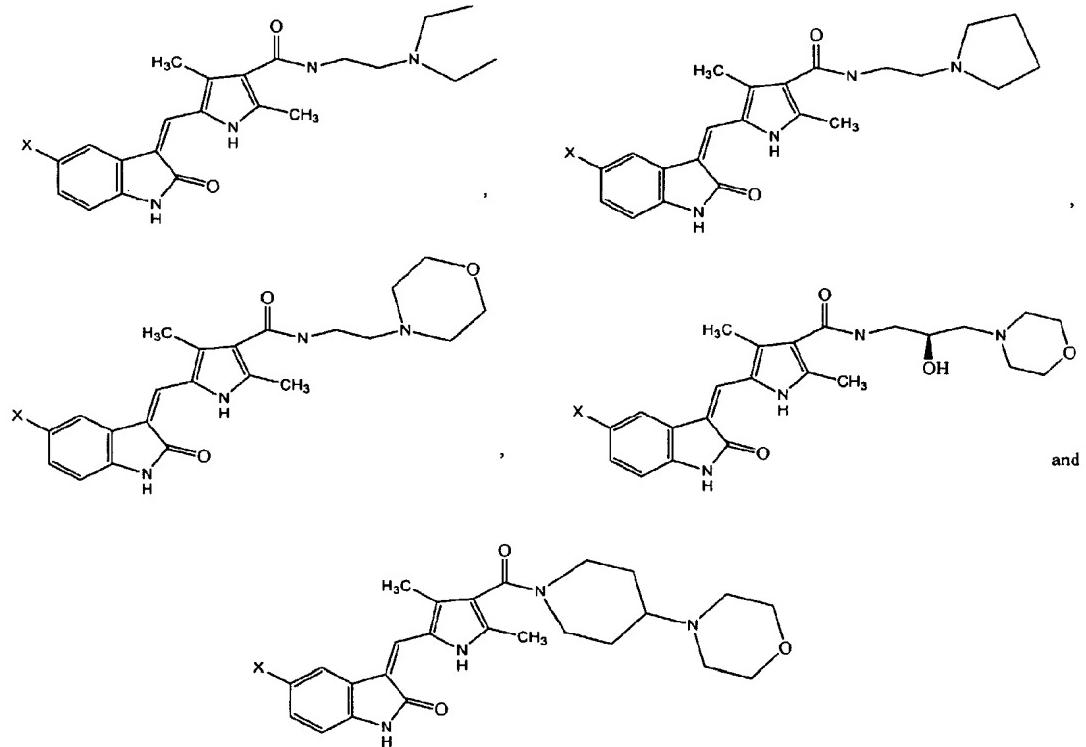
Q is C or N;

n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

20. The method of claim 18, wherein the compound that inhibits tyrosine kinase activity is selected from the group consisting of:



wherein X is F, Cl, I or Br;

or a pharmaceutically acceptable salt thereof.

21. The method of claim 18, wherein the compound of Formula I is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1).

22. A kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPCore protein

A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

23. A kit of claim 22, wherein said instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal

phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 α , IL-1 β , IL-2, NT4, GCP-2, IGFBP-1, GRO- β , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF α , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and

(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

24. A method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

(b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;

(c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

25. The method of claim 24, wherein the tyrosine kinase inhibitor is a compound of Formula I or salt thereof.

26. The method of claim 25, wherein the compound of Formula I or salt thereof is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1) or salt thereof.

27. A method of claim 24, wherein the adverse event is debilitating fatigue.

28. The method of claim 24, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one biological tissue from the mammal.

29. The method of claim 24, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

30. The method of claim 24, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

FIGURES

Figure 1.

Figure 2.

			DIFFERENCE VALUES (percent change)						
			pt 1 pre v 4 hr post d.1 200 mg/m2	pt 8 pre v 4 hr post d.1 200 mg/m2	pt 9 pre v 4 hr post d.1 200 mg/m2	pt 10 pre v 4 hr post d.1 200 mg/m2	pt 12 pre v 4 hr post d.1 200 mg/m2	pt 1 d1 pre vs 4 hr post 800 vs 200 mg/m2	pt 1 pre vs 4 hr post d1 pre-dose 200 mg/m2
			16.4	2.5	7.4	15.8	15.1	27	8.9
Cmax (ug/ml)			94.7	36.2	50.2	148.4	102.4	175.3	57.2
AUC ₀₋₂₄ (ug hr/ml)			13.2	2.2	6.6	19.8	12.5	20.6	9.7
Exposure=2.3 ug/ml (hrs)									
CLASS	spot#	pI	MW	104	12	79	16	46	204
1	5	5.79	140776						0

Difference= (1- spot% sample X / spot% sample ref)(-100)

Duplicate gels were run for each (pre and post) sample. Averaged values were used for the calculations.

- is up in post versus pre

+ is down in post versus pre

IEF with pH 4-8 ampholines. Fifty ng of IEF standard tropomyosin added to each sample before loading

SDS slab gels are 10%

Figure 3.

SPOT #	w/SU006668	MS-MS Identification	potential role
5	▼	ITIH4 (inter-alpha globulin inhibitor H4)	acute phase II.6 induced

Figure 4A.

	<i>Patient #</i>	<i>017</i>	<i>019</i>	<i>022</i>	<i>027</i>	<i>028</i>
Gene Name	Accession #	Taq/Affy F.C.	Taq/Affy F.C.	Taq/Affy F.C.	Taq/Affy F.C.	Taq/Affy F.C.
VEGF	AF022375	3.51/ND	1.49/0.8	1.68/ND	2.91/0.5	0.27/0.198
MAPK	L36719	1.14/0.65	0.26/2.56	0.75/0.67	0.54/1.96	0.21/0.39
Kinase3						
PECAM	L34657	0.72/ND	0.99/0.60	1.01/ND	0.75/0.92	0.22/0.23
Hemoglobin	AT349593	ND/1.53	ND/3.05	ND/ND	ND/3.06	ND/2.9
Epsilon 1						
Vinculin	M333208	32.19/1.96	1.43/0.75	1.71/1.21	1.84/0.62	8.24/3.72

^Normalized against 18S

F.C. = Fold Change

ND = Not detected

Table 4B.

Patient #	Taqman/Affy Fold Change	SU6668 Dose (mg/ml)	SU6668 Cmax (μg/ml)	SU6668 AUC (μg*hr/ml)	SU6668 Exposure >2.3 μg/ml (hrs)	Tumor Types
17	32.19/1.96	200 BID	11.5	66.1	11	Colon/Rectal
27	1.84/0.62	400 BID	10.3	71.2	9.1	Colon/Rectal
28	8.24/3.72	400 BID	13	164.3	21.3	Prostate

Figure 5.

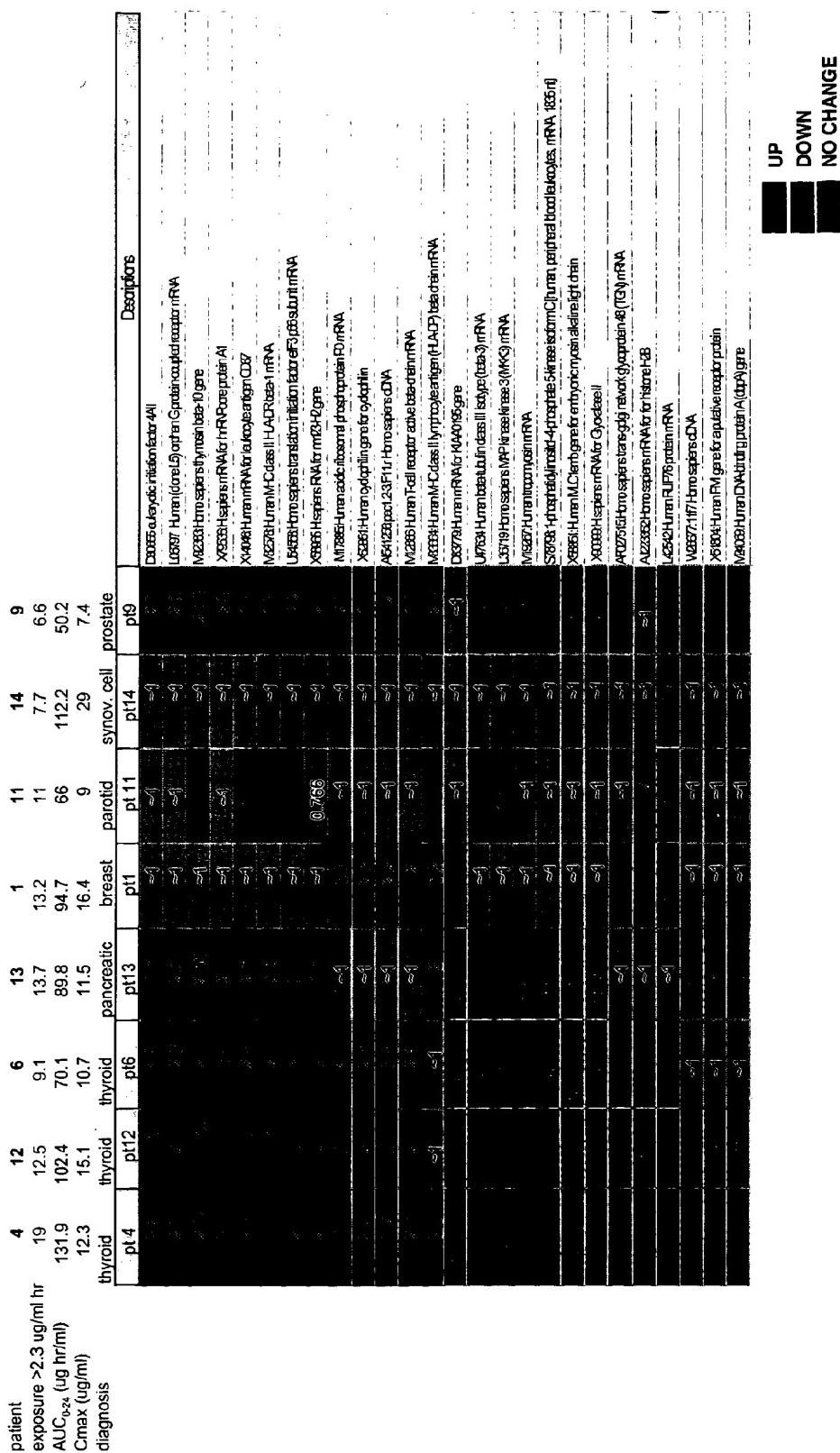


Figure 6.

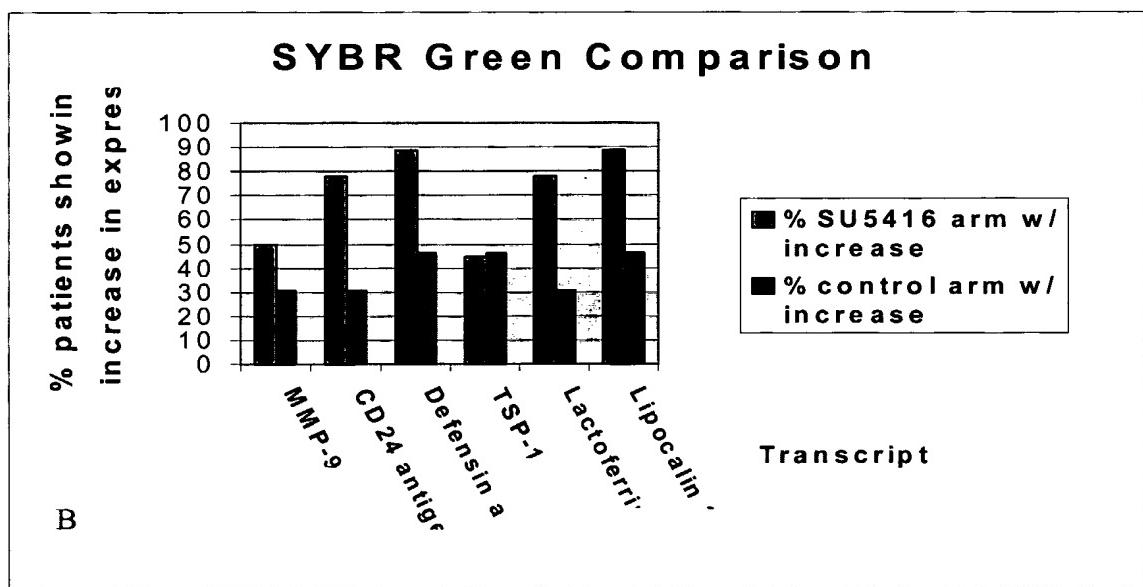
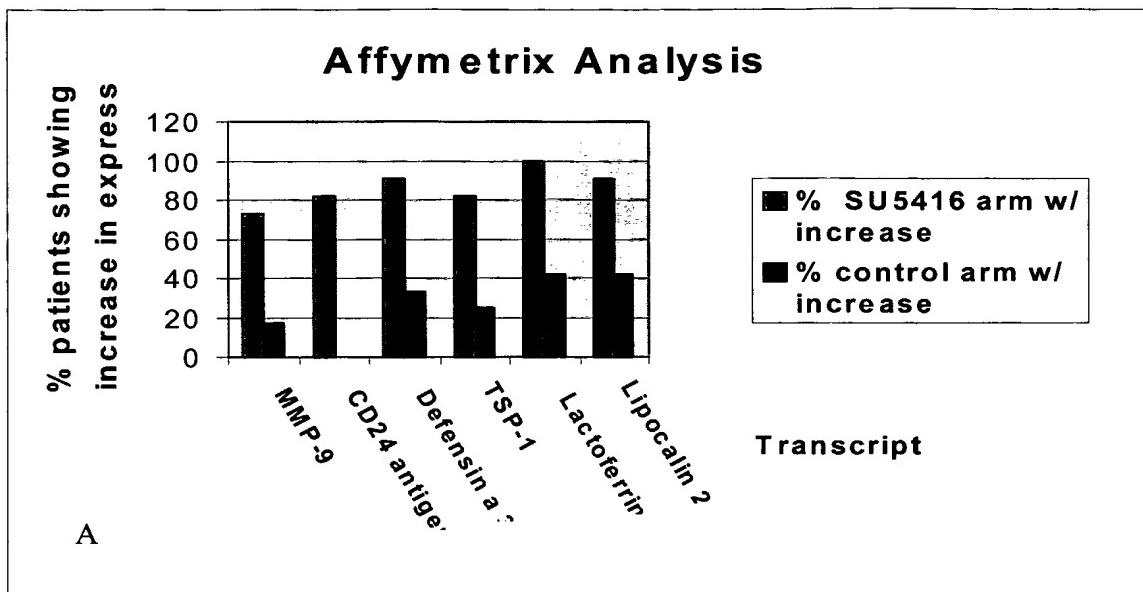
Figure 7.

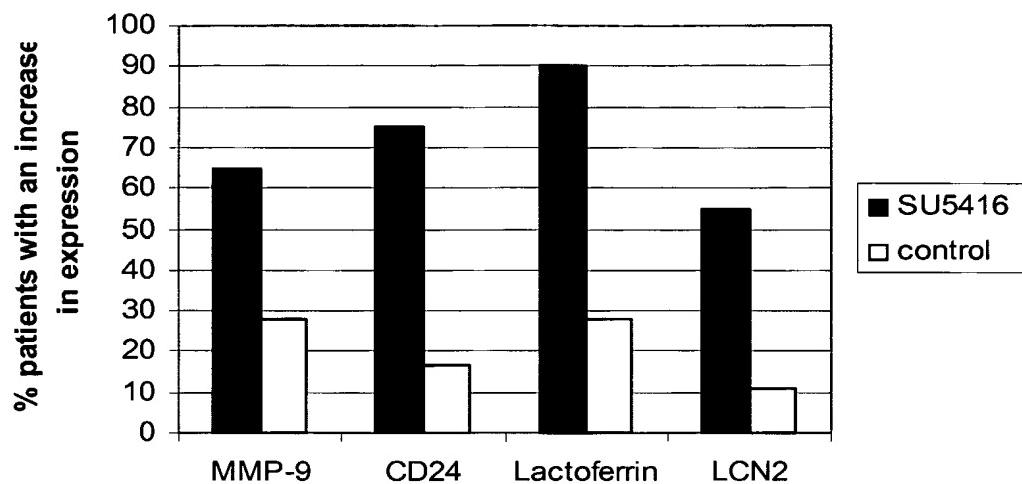
Figure 8.

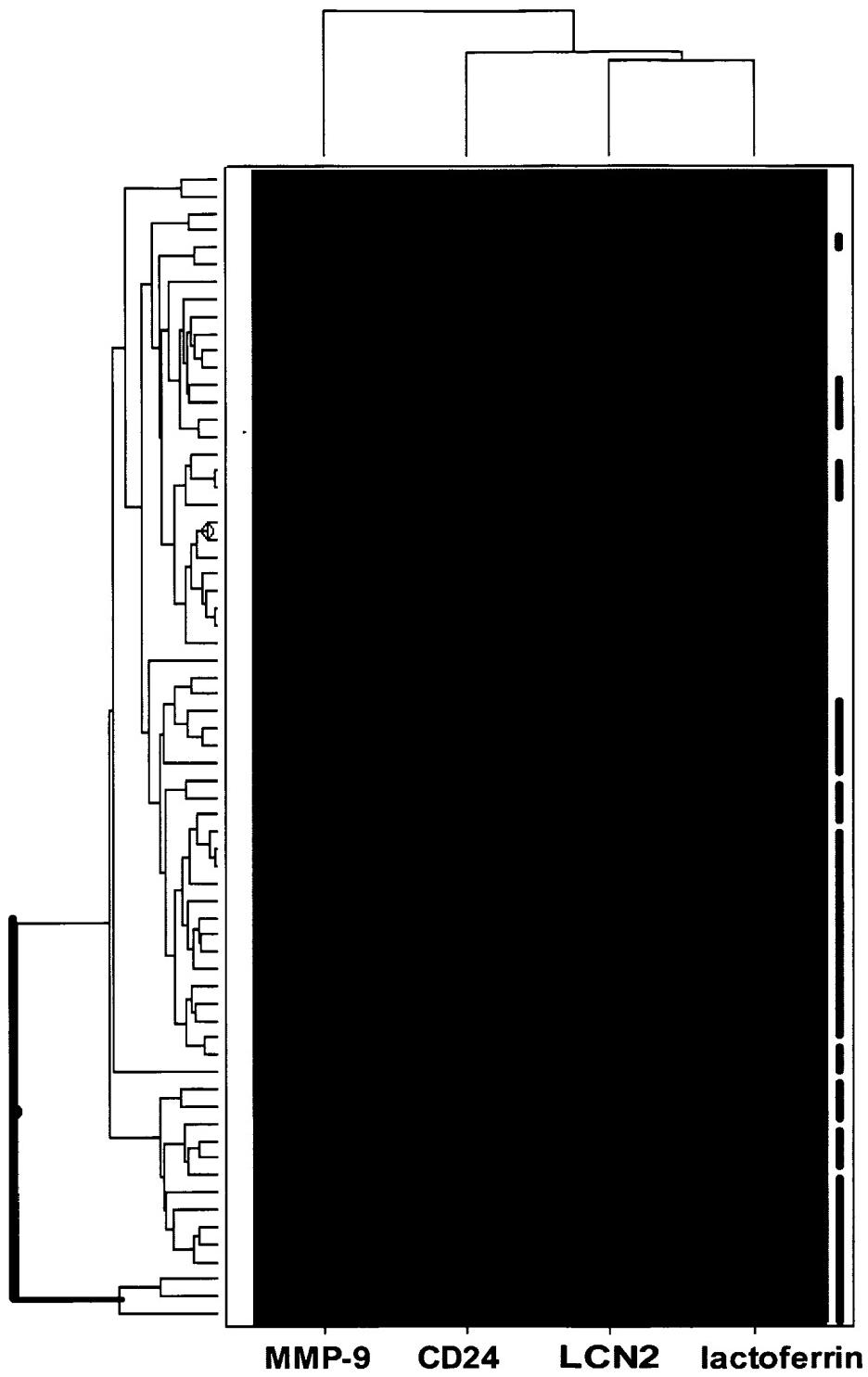
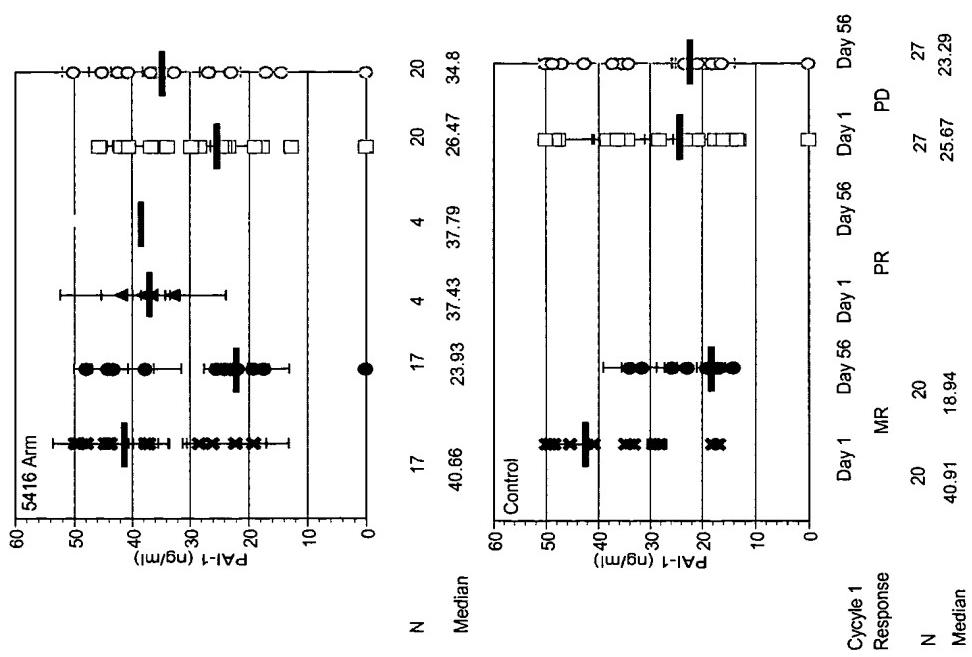
Figure 9.

Figure 10.

Median levels of PAI-1 are indicated by a solid bar.
 MR = minor response (cycle 1), PR = partial response (cycle 1), PD = progressive disease (cycle 1).

Figure 11.

mRNA and protein sequences for human lactoferrin

X53961 Human mRNA for lactoferrin [gi:34415]

1 gactcttagg ggcttcggc cctatggaa gagaaagaac atcgccggc ccaggcagaa
61 ccaggacagg tgagggtgcg ctggcgttgc ctctcgacg cgccgtgtgg gtcctgtct
121 gcctcaggc ttccggagc ctggatcc aaggaacaag tagacctggc cgccccggagt
181 ggggaggaa ggggtgtcta ttggcaaca gggccggaaa gccctgaata aaaaaaaaaaaaa
241 gggcaggcgc aagtgcagc cttcggttgc ccaagtcgc tccagaccgc agacatgaaaa
301 ctgtctcc tcgcccgtgt gttccggg gcctcggac tgggtgttgc tgccgttagg
361 agaaggagtgt tcagtggtg cggcgatattcc caacccggagg ccacaaaatg cttcaatgg
421 caaaggaaata tgagaaaatg gctggccctt cttgcagct gcataaagag agactcccc
481 atccagtgttccaggcat tgccggaaaac agggcccgatg ctgtgaccct tgatgggtt
541 ttcataacg aggaggcctt gccccctac aaactgcgc ac tctgcgc ggaagtctac
601 gggaccgaaa gacagccacg aactcactat tatgccgttgc tggtgtgaa gaaggccgc
661 agcttcacg tgaacaaact gcaagggtctg aagtccgttgc acacaggctt tcgaggacc
721 gctggatggaa atgccttac agggacactt cttccatttct tgaattggac gggccac
781 gagcccatg aggagctgtt ggcaggatc ttctcagcca gctgtgttcc cgggtcgat
841 aaaggacagt tcccaacactt gtgtccctg tgccggggaa cagggggaaa caaatgttcc
901 ttctccctcc aggaaccgtt cttccatctt ctgggttgc tcaagtgttgc gagagacggg
961 gctggagacg tggctttat cagagagacg acagtgttgc aggacacttgc agacgaggct
1021 gaaaggacg agtatgaggactt ctgcgttccca gacaacactt ggaaggccatg ggacaaatgc
1081 aaagactgccc atctggcccg ggtcccttctt catggcgatg tggcacgaaatgg
1141 aaggaggatg ccatctggaa ttctccgc caggccacagg aaaagtttgg aaaggacaaag
1201 tcaccggaaat tccagcttgc tggctccctt agtggggcaga aagatctgttgc ttcaaggac
1261 tctgcccattt ggttttcgag ggtggcccccagg agatagattt ctgggtgttgc ctttggctt
1321 ggcctacttca ctggccatccaa gaaacttggggaaaatgttggg aggaaatgttgc tgccggcgt
1381 ggcgggtcg tgggtgttgc ggtggccggag caggacttgc gcaagttaa ccagtggag
1441 ggccttggcg aaggcaggctt gacccgttgc tggcccttca ccacagagga ctgcacccgc
1501 ctgtgttgc aaggagaagc tgatggccatg agtttggatg gaggatatgtt gtacacttca
1561 tcaaatgttgc ttttgttgc tggcttgc gagaactaca aatccaaaca aagcagtgac
1621 ctgtatccaa acttgcgttgc tagacccgttgc gaaggatatac ttgtgttgc ggtggtagg
1681 agatcagaca ctggccatccaa tggaaaggca agaaggcccttgc ccacaccggcc
1741 gtggacagggaa ctggccatgc aatatcccc atggcccttgc ttctcaaccatgg
1801 tcaaatgttgc ttttgttgc tggcttgc gagaactaca aatccaaaca aagcagtgac
1861 ctgtgttgc tgggtgttgc cgacgaggcggf gagaataatgc tggccgttgc caacacca
1921 gagagataactt acggcttacac tggggcttgc cgggtgttgc ctgagaatgc tggagatgg
1981 gcattttgttgc aagatgttgc tggatccatg aacactgtatg gaaataacaa tgaggatgg
2041 gctaaggattt tgaatgttgc agacttgc tggatggcc tggatggaa acggaaatgc
2101 gtgtacttgc ctggatccatg ccatcttgc atggccggaa atcatgttgc ggtgttgc
2161 atggataagg tggaaatccatg gaaacaggatg ctgttgcacc aacaggctaa attttgg
2221 aatggatctg acttgcgttgc caagtttgc ttatccatg ctggaaaccaa aaccccttgc
2281 tcaatgaca acacttgc tggccatgc ctggccatgc aacacacata tggaaaatata
2341 tggggaccac agatgttgc agccattactt aatctgaaaaa atgtgttgc ac cttccccc
2401 ctggaaatccatg tggatccatg cggatggaa accggaaatgg gatggcccgat cttccca
2461 aaccccttgc catttgc cccatgttgc tggatggcc tggatgggg ctttggctt
2521 ctgtgttgc tggggatgg cccatccatg tggatggcc tggatggcc tggatgggg
2581 agaagttttt tgagaaaatggatattt caaaaaaaaaaaaa

Protein sequence of human lactoferrin

MKLVFLVLLFLGALGLCLAGRRLRSVQWCAVSQPEATKCFQWQR
NMRKVRGPPVSCIKRDSPICQCIQIAENRADAVTLDGGFIYEAGLAPYKLRPVAAEVY
GTERQPRTHYYAVAVVKGGSFQLNELQGLKSCHTGLRRTAGWNVPTGTLRPFLNWTG
PPEPIEAAVARFFSASCVPGADKGQFPNLCLRCAGTGENKCAFSSQEPIFSYSGAFKC
LRDGAGDVAFIRESTVFEDLSDEAERDEYELLCPDNTRKPVDKFKDCHLARVPSHAVV
ARSVNGKEDAIWNLRRQAQEKFGKDKSPKFQLFGSPSGQKDLLFKDSAIGFSRVPPRI
DSGLYLGSGYFTAIQNLRKSEEEVAARRARVVWCAVGEQELRKCNQWSGLSEGSVTCS
SASTTEDCIALVLKGEADAMS LDGGYVYTACKCGLVPVLAENYKSQQSSDPDNCVDR
PVEGYLA VAVVRRSDTSLTWNSVKGKKSCHTAVDRTAGWNIPMGLLFNQTGSCKFDEY
FSQSCAPGSDPRSNL CALCIGDEQGENKCVPSNERYGYTGAFRCLAENAGDVAFK
DVTVLQNTDGNNEAWAKDLKLADFALLCLDGKRKPVTEARSCHLAMAPNHAVVSRMD
KVERLKQVLLHQAKFGRNGSDCPDKFCLFQSETKNLLFDNDTECLARLHGKTTYEKY
LGPQYVAGITNLKKCSTSPLLEACEFLRK

mRNA and protein sequences for human lipocalin-2 (LCN2)

NM_005564

Homo sapiens lipocalin 2 (oncogene 24p3) (LCN2), mRNA [gi:5031852]

1 atgccccctag gtctcctgtg gctgggccta gcccgttgg gggctctgca tgcccgaggcc
61 caggactcca cctcagacccat gatccagcc ccacctctga gcaaggccc tctgcagcag
121 aacttcagg acaacaatt ccaggagaag tggatgtgg taggcctggc agggaatgca
181 attctcagag aagacaaaaga cccgaaaaag atgtatgcca ccacatctatga gctgaaagaa
241 gacaagagct acaatgtcac ctccgtccctg tttagaaaaa agaagtgtgc ctactggatc
301 aggacttttg ttccagggtt ccagccggc gagttcacgc tggcaacat taagagttac
361 cctggattaa cgagttaccc tggccggatgt gtgagccacca actacaacca gcatgctatg
421 gtgttcttca agaaagggttcc taaaacagg ggttacttca agatcacccctt ctacgggaga
481 accaaggagc tgacttggaa actaaaggag aacticatcc gtttctccaa atatctggc
541 ctccctgaaa accacatctg tcctccctgtc ccaatcgacc agtgtatcga cggttgc

Note: there is an additional 3' exon, not represented in the mRNA sequence above, that is included in the sequence that Affymetrix used in designing probes for LCN2 expression (and which was used in designing RT-PCR primers). The additional sequence is as follows:

1 ggtgccgcca gctgccgcac cagccccgaac accattgagg gagctggag accctccccca
61 cagtgcacc catgcagctg ctcccccaggc caccggctgt atggagcccccc accttgcctg
121 ctaaataaac atgtgc

Protein sequence for human lipocalin-1 (LCN2)

MPLGLLWLGLALLGALHAQAQDSTSDDLIPAPPLSKVPLQQNFQD
NQFQGKWYVVGLAGNAILREDKDPQKMYATIYELKEDKSYNVTSVLFRKKCDYWIRT
FVPGCQPGEFTLGNIKSYPLTSLVRVVSTNYNQHAMVFFKKVSQNREYFKITLYGR
TKELTSELKENFIRFSKYLGLPENHIVFPVPIDQCIDG

mRNA and protein sequences for human MMP-9

NM_004994 **Homo sapiens matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase) (MMP9), mRNA [gi:482835]**

1 agacacctct gccctcacca tgagccctcg gcagccccgt gcctcgggtgc tcctgggtct
61 gggctgctgc ttgtgccc ccagacagcg ccagtccacc ctgtgcctct tccctggaga
121 cctgagaacc aatctcaccg acaggcagct ggcagaggaa tacctgtacc gctatggta
181 cactcgggt gcagagatgc gtggagagtc gaaatctcg gggccctgc tcgtctct
241 ccagaagcaa ctgtccctgc ccgagacccgg tgagctggat agcgccacgc tgaaggccat
301 gcbaacccca cggfgccccgg tcccgacccct gggcagattc caaaccttgc agggcgcacct
361 caagtggcac caccacaaca tacccatttgc gatccaaaact tactcggaaag acttgcgcgc
421 ggcgggtatt gacgacgcct ttgcggcgc ctgcacttg tgagcgcgg tgacgcgcct
481 cacccact cgcgtgtaca gccccggacgc agacatcgatc atccagtttgc tggtgcgg
541 gcacggagac gggttacccct tcgacgggaa ggacgggcgc ctggcacacgc ctttcctcc
601 tggccccggc attaggggag acgcatttgc acgcgtac gagttgtgttgc cctggcaca
661 gggcgtcgatgttcaactc ggttggaaa cgacatggc gggcgcgc acitcccttgc
721 catctcgag ggccgcctct actctgcctgc caccacggc ggtgcgcctcg acggcgttgc
781 ctggcgttgc accacggcca actacgacac cgacgaccgg ttggcttgc tccccagcga
841 gagactctac acccgggacg gcaatgtga tggaaaccc tgcgcgttgc cattcatcttgc
901 ccaaggccaa tcctactccg cctgcaccac ggacgggtgc tccgacggct acggcgttgc
961 cgccaccacc gcaactacg accgggacaa gctcttcggc ttctgcccgc cccgagctga
1021 ctgcacggtg atggggggca actcggcggg ggagctgtgc tcgttcccttgc tcaacttcttgc
1081 gggtaaggag tactcgaccc tgcacagcga gggccggcggatggggcgcct tctggcgcgc
1141 taccacccctcg aacttgcata ggcacaagaa gtggggcgc tgcgggacc aaggatacag
1201 ttgttcctc gtggggcgc atgagttcgcc acacgcgtcg ggettagatc attcctcgt
1261 gccggaggcg ctcatgtacc ctatgtacc ctgcacttgag gggccccct tgcataaggaa
1321 cgacgtaat ggcatccggc acccttatgg tcctgccttgc gaacctgagc cacggccctc
1381 aaccaccacc acacccgcgc ccacggcgtcc cccgacggc tgcgggacc gaccggccac
1441 tgcacccctcg tcagagcgc ccacagctgg ccccacaggt ccccccctcag ctggcccccac
1501 aggccccccct actgtggcc ctctacggc cactactgtg ctgttgc ggggggggg
1561 tgcctgcacca gtaacatct tcgacgccttgc cggggagatt gggaccggc tgcgttgc
1621 caaggatggg aagtactggc gatctctgc gggcagggggg agccggccgc agggccccct
1681 ccttacgc gacaagtgcc cccgcgtgc cccgcacaggt gactcgggttgc ttggaggac
1741 gcttcacca gaaatcttgc tcttctgc ggcggcagggtg tgggtgtaca caggcgcgc
1801 ggtgtggc cccggggcgc tggacaaggt gggcctggg gccgacgtgg cccagggtgac
1861 cggggccctc cggagttggca gggggaaagat gctgtgttc agcggggccgc gcctctgg
1921 gttcgaatgt aaggcgcaga tgggtgtatcc cccggggcgc acggggatgg accggatgttgc
1981 cccgggggttgc ctgttgc gacaacgcgt ctccagatc cgggggggg
2041 ccaggaccgc ttctactggc ggtgtgttgc cccggggatgg tgaaccagg tggaccaat
2101 gggctacgttgc acctatgaca tcctgcgttgc ccctggggac tagggcgtcc gtcctgttgc
2161 gcagtgccat gtaaaatccccctt actggggacca accctgggggaggaggcgttgc
2221 caaaatgttgc ttctgttgc gaggaaaggaggaggatgggatggggcgttgc
2281 tcaccccttgc tttttgttgc agtgttctatataacttgg attctctaacttgc

Protein sequence for Homo sapien MMP9

MSLWQPLVLVLLVLGCCFAAPRQRQSTLVLPGDLRTNLTDRQL
AEEYLRYGYTRVAEMRGESKSLGPALLLQKQLSPETGELDSATLKAMRTPRCGVP
DLGRFQTFEGDLKWHHHNITYWIQNYSEDLPRAVIDDAFARAFALWSAVTPLTFTRVY
SRDADIVIQFGVAEHGDGYPDFGKDGLLAHAFPPGPGIQQGDAHFDDDELWSLGKGVVV
PTRFGNADGAACHFPFIFEGRSYSACTTDGRSDGLPWCSTTANYDTDDRFGFCPSERL
YTRDGNADGKPCQFPFIFQGQSYSACTTDGRSDGYRWCAATTANYDRDKLFGFCPTRAD
STVMGGNSAGELCVFPFTFLGKEYSTCTSEGRGDGLWCATTNSFDSDKKWGFCPDQG
YSLFLVAAHEFGHALGLDHSSVPEALMYPMYRFTEGPLLHKDDVNGIRHLYGPRPEPE
PRPPTTTTPQPTAPPTVCPTGPPTVHPSERPTAGPTGPPSAGPTGPPTAGPSTATTVP
LSPVDDACVNIFDAIEIGNQLYLFKDGYWRFSEGRGSRPQGPFLIADKWPALPRK
LDSVFEEPLSKKLFFFSGRQVWVYTGASVLGPRRLDKLGLGADVAQVTGALRSGRGKM
LLFSGRRLWRFDVKAQMVDPRSASEVDRMFPGVPLDTHDVFQYREKAYFCQDRFYWRV
SSRSELNQVDQVGYVTYDILQCPED

mRNA and protein sequences for human CD24

L33930 **Homo sapiens CD24 signal transducer mRNA, complete cds and 3' region [gi:500848]**

Protein sequences for human CD24

MGRAMVARLGLGLLLALLLPTQIYSSETTGTSSNSSQSTSNS
GLAPNPTNATTKAAGGALQSTASLFVVSLSSLHLYS

Figure 12. (Page 1 of 33)

D30655. Homo sapiens mRNA...[gi:485387]:

Eukaryotic initiation factor 4AII

DNA sequence:

protein sequence:

MSGGSADYNREHGGPEGMDPDGVIESNWNEIVDNFDDMLKESLLRGYIAYGFEKPSAIQQRAIIPCIKGVDVIAQAQ
SGTGTATFAISILQQLEIEFKETQALVLA
TPGRVFDMLNRRYLSPKWIKMFVLDEADEMLS
KKEELTLEGIKQFYINVEREEWKLDL
REFRSGSSRVLITTDLLARGIDVQQVSLV
EMPMNVADLI

Figure 12. (Page 2 of 33)M92383. Homo sapiens thym...[gi:339696]:

Homo sapiens thymosin beta-10 gene

DNA sequence:

1 cgtcctacat ctgcgcata cacgcccacg tgccacatc actggggtg ccncggaga
61 cagagccgct ggtggctaa ggnggggggg cagccaggag aaagccccgc cgctgctcg
121 cccgccccctc ggggtccagc accgccccctg ctggccggg tgagggccgg ggcggggccg
181 cggcgtatata aaggcttaggc ggggcgcgc tcctttgtt ctgttgtcga caacgcgagt
241 gggagcacca ggatctcggg ctccgaacga gactgcacgg tgacgtgacg gccggccgg
301 ggcggcagggt gtggtcggat cccgtgcacc gcgggcgcgc aacccggaca ggcgttctc
361 ggacccggacg caggggccgc gaccacgccc tgggaccgag aagaggggtt cggacgcgc
421 cagatccctcg gccttgggc tgctcgccag ccttggcgcg agtgccacgt cgagaggcg
481 cggcggggag cgccgaaggg gacggcgtgc gcccaggccc aggtcaagcg ccttggttt
541 cccacttagga ttgttttaag aaaatggcg acaaaccaga catggggaa atcgccagct
601 tcgataaggc caagtcgaag aaaacggaga cgcaggagaa gaacacctg ccgaccaaag
661 agagtggatg tgccctcggtc tccgcgccttcc agcccgccccc ctcaccctgc tcttcctgc
721 aaacccactc ctccacccccc caccggcccg ttgtccccgg tgccggccgc cccggcactc
781 ttcagtttc acaaaaggcc ttgtttctcc ccagccctaa gcitccctctt aaatccaca
841 cctcggtgt ctcatcacac cgggaagcac ctccgttgcg ggtgggggt tgccagcnccc
901 ctccagcgcc cccgttcgtc tcaagccatt gagcaggaga agcggagtga aatttcctaa
961 gatccctggag gatitccctac ccccccgtc tcggagcacc ccagtgcgt atgtggagaa
1021 gagccaccct gcaagatgga cacgagtcca caagctgcac tggtaaacctg cgagccgc
1081 ccgalgccac cggccgtgg tcgtctgaag ggacccccc ccaatcgac tgccaaattc
1141 tcggtttgcc cccggatatt ataaaaattt atttgtatga ataatggaaa taaaacacac
1201 ctctggca tggctggcg tggcttgatgt gtttagtta gtatgggtgc agtccactgc
1261 ag

protein sequence:

DCFKKMADKPDMDGEIASFDKAKLKKTETQEKNLPTKETIEQEKRSEIS

Figure 12. (Page 3 of 33)X79536. H.sapiens mRNA fo...[gi:496897]:

H.sapiens mRNA for hnRNPCore protein A1

DNA sequence:

1 ttaaagtctc tcttcaccc gccgtcatgt ctaagtcaaga gtctccaaaa gagccccaaac
61 agctgaggaa gcttccatt ggagggttga gcttggaaac aactgtatgg agccctgagga
121 gccatttga gcaatgggaa acgcacacgg acttgtgtt aatggagat ccaaacaccca
181 agcgcttag gggcttggg ttgtcacat atgccactgt ggaggagggtg gatgcagcta
241 tgaatgcacgg gccacacaag gtggatggaa gagttgtggaa accaaagaga gctgtctcca
301 gagaagatc tcaaagacca ggtgcccact taactgtgaa aaagatattt gttgggtggca
361 ttaaagaaga cactgaagaa catcacctaa gagattttt tgaacagtat gaaaaattt
421 aagtgtatgtt aatcatgact gaccgaggca gtggcaagaa aaggggcattt gcctttgtaa
481 ccttgacga ccatgactcc gtggataaga ttgtcattca gaaataccat actgtatg
541 gccacaactg tgaaggtaga aaagccctgt caaagcaaga gatggctagt gcttcattcca
601 gccaaagagg tcgaagggt tctggaaact ttgggggttgc tctggaggt ggttccgggt
661 ggaatgacaa ctccggcgtt ggagggaaact tcagttggcg tggggctt ggtggcagcc
721 gtgggggttgc tggatgttgg ggcagtgggg atggctataa tggatggc aatgtatggaa
781 gcaattttgg aggtgggttgc agctacaatg attttggaa ttacaacaat cagtctcaa
841 attttggacc catgaaggaa ggaatttttgg gaggcagaag ctctggcccc tatggcggtt
901 gaggccataa ctggccaaaa ccacggaaacc aagggtggctt tggcggttcc agcagcagca
961 gtatgtatgg cagtggcaga agatgtttaat tagggaggag tctgtacta gtcattatcag
1021 ctctaaaaaa cagaaactca tctgttccaaatg ttctggcag aaagggacgt cttgttgc
1081 acctttatct gagccactgt acttcgttat cacggccatgc agtttacatg agctgttgc
1141 cagctcgaaa ttccattttt tgaatgggtt ttttttttta ataaactgtt tttactt

protein sequence:

MSKSESPKEPEQLRKLFIGGLSFETTDESLRSFHEQWGTLTDCVVMRDPTKRSRGFGFVTYATVEEVDAAMNARP
HKVDGRVVEPKRAVSREDSQRPGAHLTVKKIFVGGIKEDTEEHHLRDYFEQYGKIEVIEIMTDRGSGKKRGFAFVTFD
DHDSVDKIVIQKYHTVNGHNCEVRKALSKQEMASASSQGRSGSGNFGGGRGGFGGNDNFGRGGNFSRGGF
GGSRGGGGYGGSGDGYNGFGNDGSNFGGGGSYNDFGNYNNQSSNFGPMKGGNFGGRSSGPYGGGGQYFAKP
RNQGGYGGSSSSSSYGGSRFF

Figure 12. (Page 4 of 33)X14046. Human mRNA for le...[gi:29793]:

Human mRNA for leukocyte antigen CD37

DNA sequence:

1 gctccccca ctgtcagcac ctcttcgtg tggtagtg accgcttacc ccactaggtg
61 aagatgtcag cccaggagag ctgcctcagc ctcatcaagt acttcctctt cgtttcaac
121 ctcttctct tcgtccctcg cagcctgatc ttctgcttcg gcatctggat cctcatcgac
181 aagaccagct tcgtgtcctt tggggcttg gcctcgtgc ctctgcagat ctggtccaaa
241 gtcctggcca tctcaggaat cttcaccatg ggcacatcgccc tccctgggttg tggggggcc
301 ctcaggagc tccgtgcctt cctggggcttg tattttggga tgctgctgctt cctgttgcc
361 acacagatca cccggaaat cctcatctcc actcagcggg cccagctgga ggcggcttgc
421 cgggacgtcg tagagaaaaac catccaaaag tacggcacca accccgggaa gaccggcc
481 gaggagagct gggactatgt gcagttcccg ctgcgtgc gggctggca ctacccgcag
541 gactggtcc aagtccat cctgagaggt aacgggtcg aggccgcaccc cgtgcctgc
601 tccgtctaca acttgtcgcc gaccaacgcac tccacaatcc tagataaggat gatcttgccc
661 cagctcagca ggctggaca ctggcgccgg tccagacaca gtgcagacat ctgcgtgtc
721 cctgcagaga gcccacatcta ccggcgaggc tgccgcgcagg gcctccagaa gggctgcac
781 aacaacctta ttccatagt gggcattgc ctggcgctcg gcctactcga gctcgggttc
841 atgacgcctct cgatattctt tgccggaaaac ctggaccacgc tctacaacccg gctcgctcga
901 taccgtttagg ccccccctc cccaaagtcc cggccggcc cggcacgtg cgctgggcac
961 ttccctgtcg ctgttaataa ttgtttaaat ccccgatcgc ctggagccc tccgcctca
1021 cattccccctg gggacccacg tgccgtcgcc cccctgcgtc tgccaccccccacgggac
1081 ctggggctt cgtccacacg tccctgtccc catctgtcg cctac

protein sequence:

MSAQESCLSLIKYFLFVFNLFVNLFFFVLGSLIFCFGIWILIDKTSFVSFVGLAFVPLQIWSKVL AISGIFTMGI ALLGCVGALKEL
RCLLGLYFGMLLLLFATQITLGILISTQRAQLERSLRDVVEKTIQKYGTNPEETAEEESWDYVQFQLRCCGWHYPQDW
FQVLILRGNGSEAHRVPCSCYNLSATNDSTILDKVILPQLSRLGHLARSRHSADICAVPAESHIYREGCAQGLQKWLN
NLISIVGICLGVLLELGFMTLSIFLCRNLDHVYNRLARYR

Figure 12. (Page 5 of 33)M32578. Human MHC class I...[gi:188305]:

Human MHC class II HLA-DR beta-1

DNA sequence:

1 agttctccct gagtgagact tgccigctcc tctggcccct ggtccgttcc tggccat
61 catggtgtt ctgaagctcc ctggagggttc ctacatggca gtgtcgacag tgacactgt
121 ggtgctgagc tccccactgg ctttggctgg ggacacccga ccatgtttct tgacggc
181 taagtatgg tgcattctc tcaacggggac ggagcgggtg cggtccctgc acagaggcat
241 ctataaccaa caggagaacg tgcgcgttca cagcgacgtg ggggagttacc gggcggtgac
301 ggagctgggg cggcctgacg ctgagttactg gaacagccag aaggacatcc tggagcaggc
361 gcggggccgc gggcacacct actcgacaca caactacggg gctgtggaga gcttcacagt
421 gcagcggcga gtggaccta aggtgactgt gtatcctgca aggaccaga ccctgcagca
481 ccacaaccc tcggctctgt ctgttaatgg ttcttatcca ggcagcatgg aagtccagg
541 gtccggaaac ggccaggaag agaaggctgg ggtgggttcc acaggcctga ttccaaatgg
601 agactggacc ttccagattc tgggtatgtt gaaaaacaggctt cctcggagatg gagaggat
661 cacctgccaat gtggagcacc caagcgtgac gagcccttc acagtggaaat ggagagcaca
721 gtctgaatct gcacagagca agatgttgc tggaaatcggg ggctttgttc tggccctgt
781 ctccctggg gccgggctat tcatctactt caagaatcgaa aaaggccact ctggacttca
841 cccaaacagga ctcgtgactt gaagtgcaga tgaccacattt caagggggaa ctttctgcc
901 cagcttgc tggaaaatg ctccctgtt tggcttctt tttccacaa gagaggact
961 ttcaggcccc tgggttgc tgggttgc actctgcaga aaatgtccat ctttgc
1021 tcctcagctc ctggccctgg cctgaagtcc cagcatgtat ggcagtgcct catctcaac
1081 tttagtgctc ccctttaactt aaccctacgg cctccatgc atctgttactt cccctgtgcc
1141 acaaatggac tacgttattt aattttctt aagcccaagag taaaaatca tctgtccacc
1201 tggcacaaaa gacaaa

protein sequence:

MVCLKLPGGSYMAVLTVTLMVLSPLALAGDTRPCFLQQDKYECCHFFNGTERVRFLHRGIYNQQENVRFDSDVGEY
RAVTELGRPDAEYWNSQKDILEQARAADVDTYCRHNYGAVESFTVQRRVEPKVTVPARTQTLQHHNLLVCSVNGFY
PGSIEVRWFRNGQEEKAGVVSTGLIQNGDWTFQILVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRAQSESAQSKM
LSGIGGFVLGLLFLGAGLFYFKNQKGHSGLHPTGLVS

Figure 12. (Page 6 of 33)

U54558. *Homo sapiens* tran...[gi:2351377]:

Homo sapiens translation initiation factor eIF3 p66 subunit mRNA

DNA sequence:

Protein sequence:

MAKFMTPTVIQDNPSPGWGPGCAVPEQFRDMPYQPFSGKDRLGKVADWTGATYQDKRYTNKYSSQFGGGSQYAYFHE
EDESSFQLVDTARTQKTAYQRNRMRFAQRNLRRDKDRRNMLQFNLQILPKSAKQKERERIRLQKKFQKQFGVRQKW
DQKSQKPRDSSVEVRSDWEVKEEMDFPQLMKGMRYLEVSEPAQDIECCGALEYYDKAFDRITTRSEKPLRSIKRIFTVT
TTDDPVIRKLAKTQGNVFATDAILATLMSCTRSVYSDIVQRVGSKLFFDKRDNSDFDLTVSETANEPPQDEGSNF
NSPRNLAMEATYINHNFSSQQCLRMGKERYNFPNPVEDDMDKNEIASVARYRRWKLGDDIDLIVRCEHDGVMT
GANGEVSFINIKTLNEWDSRHNCNGVDWRQKLDQSQRGAVIATELKNNSYKLARWTCCALLAGSEYKLGYVSRYHVKD
SSRHVLGTTQZQFKPNEFASQINLSVENAWGILRCVIDICMKLEEGKYLILKDPNKQVIRVYSLPDGTFSDEEEEEEEE
EEEEEEET

Figure 12. (Page 7 of 33)X58965. H.sapiens RNA for...[gi:35069]:

H.sapiens RNA for nm23-H2 gene

DNA sequence:

```
1 cggccacgag gcggaatccc ttctgcgttc ccagcgcagc gcccggccc ggccccctcca
61 gcttcccgga ccatggccaa cctggagcgc accttcatcg ccatcaagcc ggacggcggt
121 cagcggggcc tggggggcga gatcatcaag cgcttcgagc agaaggggatt ccgcctcggt
181 gccatgaagt tcctccgggc ctctgaagaa caccctgaagc agcactacat tgacctgaaa
241 gaccgaccat tcctccctgg gctggtaag tacatgaact cagggccgggt tggccatg
301 gtctgggagg ggctgaacgt ggtgaagaca ggccgagtga tgctggggg gaccaatcca
361 cgacatcaa agccaggcac cattcgtggg gacttcgtca tcagggtgg caggaacatc
421 attcatggca gtgattcagt aaaaagtgtc gaaaaagaaa tcagcctatg gtttaagct
481 gaagaactgg ttgactacaa gtctgtgtc catgactggg tctatgaata agagggtggac
541 acaacacgag tcctccctcag cacggcgtgg tggtccctg gacacagctc tcattccat
601 tgacttagag gcaacaggat tgatcattct ttatagacg atattgcca ataaagctt
661 tggaaagccgg
```

protein sequence:

```
MANLERTFIAIKPDGVQRGLVGEIIRFEQKGFRLVAMKFLRASEEHLKQHYIDLKDRPFFPGLVKYMNSGPVVAMVV
EGLNVVKTGRVMLGETNPADSKPGTIRGDFCIQVGRNIIHGSDSVKSAEKEISLWFKPEELVDYKSCAHDWVYE
```

Figure 12. (Page 8 of 33)

M17885. Human acidic ribo...[gi:190231]:

Human acidic ribosomal phosphoprotein P0 mRNA

DNA sequence:

1 cttctctcgccaggcgtct cggtggaaatg acatcgctt taaaacccctt cggtggcaatc
61 cctgcacgcac cgccgtgtatg cccaggaaag acaggggcgc acgtggatcc aactacttcc
121 ttaagatcat ccaactattg gatgattatc cggaaatgttt catgtggaa gcagacaatg
181 tgggtccaa gcagatgcag cagatccgc tggccctcg cgggaaggct gtgggtgtga
241 tggcaagaa caccatgtatgc ccaaggccca tccgaggccca cctggaaaac aaccaggctc
301 tggagaaact gtcgcctat atccggggaa atgtgggtt tgcgttcacc aaggaggacc
361 tcactgatc caggacatgt tgctggcca ataagggtgcc agtcgtgc cgtgtggtg
421 ccattggcccc atgtgaagtc actgtggccag cccagaacac tgggtctggg cccgagaaga
481 cctccctttt ccaggctta ggtatcacca ctaaaatctc caggggcacc attgaaatcc
541 tgagtgtatgc cagactgtatc aagactggag acaaagtggg agccagcgaa gccacgcgc
601 tgaacatgtt caacatctcc ccccttcctt ttgggttgtt catccagcgatgttgcaca
661 atggcagcat ctacaaccctt gaagtgtt atatcacaga ggaaactctg cattctcgct
721 tcctgggggg tgcgtccaaat gtgcgtgtt tgcgttcgc gatggctac ccaactgttg
781 catcgttacc ccatcttatac tcaacgggtt acaaacgggtt cctggccttg tgcgtggaga
841 cggatttacac ctcccaactt gtcggaaagg tcaaggccctt ctggcgtat ccatctcgctt
901 ttgtggctgc tgccctgtt gtcgtccaaat ccacagctgc tccgtcgct gtcgtcc
961 cagctaagggt tgaaggccaaat gaaggtcggtt aggagtccgtt cggaggatgtt ggattttggc
1021 tcttttactatcaccaaaa agcaaccaac ttagccgtt ttatgttgc aacaaggaaaa
1081 taaaaggctt ctccctt

protein sequence:

MMPREDRATWKSNYFLKIIQLLDDYPKCFIVGADNVGSQMQQQIRMSLRGKAVVLMGKNTMMRKAIRGHLENNPALEK
LLPHIRGVGFVFTKEDLTEIRDMLLANKVPAAARAGAIAPCEVTVPQAQNTGLGPEKTSFFQALGTTKISRGTEIILSDV
QLIKTGDKGVGASEATLLNMLNISPFSGVLVIQQVFNDGSIYNPVEVDITEETLHSRFLEGVRNVASVCLQIGYPTVASVP
HSIINGYKRVLALSVERDYTFPLAEVKAFALDPSAFVAAAPVAAATTAAAPAAAAAPAKVEAKEESEESDEDMGFGLFD

Figure 12. (Page 9 of 33)

X52851. Human cyclophilin...[gi:30167]:

Human cyclophilin gene for cyclophilin

DNA sequence:

1 gaattccctt gtaagggttt ctaacaaaa caccagtcac ataagtgcac ttatattat
61 atttttgtt attatttgta gacggagct ctgtctctc aggctggagt gcagtggcgc
121 catctgcgct cgctcaacc tccacctctt gggttccagc gattctctt ctcagccct
181 ccgagggggtt agctggact acagggtgc accaccatgc ccagctaatt tttttttttt
241 cgttagatgtt gggtttaccat atgtgtcca ggctggctt gaactcttga ctcagggttga
301 tcctccgc tccgcctccc aaagtgcgg aattacaggc gtatccacc gcacccggcc
361 ttttttgta gagagggtca cactctgtcg tcccgctgg aatgcagtga tgcatcacc
421 gcccactaca gcctgcacctt ccgggtcaaa gcaatccccc ccccccagcc tccgttagtg
481 cgagcgccctc gacgccccagc taattttttt tttttttttt tttttttttt tttttttttt
541 tctcttaaatgat gcccaggctg gtggccgggg tcaactctt aagatgaagc gatccccc
601 ggccttggcc tccgcgcctc taaaagcgcc aggtatgagc caccgcgcctt ggcctacaag
661 tgcatttaa ttaaagtattt attaatgtct ttgcctgaag aaattcgctt ttaaatttgt
721 acttatctt cacccaaaaaaa tcaaaagcaca attcagcccc gaggcggggg cggtaggagc
781 tggcgccggc gggggcaggg aaagaccagg agcagagatt caaaaagagt aagagggcaa
841 aatgtgcata atgcataatc acaggtaaga gcctggccag gctctgttt taatggcttc
901 ctctgaaga agatcaagc agagtgttaag atatttcgg aaagttagagc atttgtt
961 catttcataaa tctctaaaaa ccggagactg ctccgtccc acctcgtagt agaaaaacagc
1021 gatgtcaaa ggcaaccctcc ttccgtacat tgccctggtag gacgcgacgtt ggttgttgc
1081 cgcgcgaaat gcccggacgaa ggctgcctt aggtctcggtt gacgcgccccat ccccttcc
1141 gctcgcggag gctgtgggtt cggcgccggg acccccagtcg accttgcactg gccggccgc
1201 ctgtggccct gctgtccctt cttgtgtcaaa tggggagacg cccctcatcg
1261 ctgtacaacg gcccggacg cccctggccctt ccgtctcccg cttgtgtccgg ccatgtgtcc
1321 cacccttccgtt ccgcactgac cttcccccgtt gccccggccgtt ccgtactgtcc gccccggcc
1381 gagtccccatg ccgcggccac cgcgacggag cccggcaggccg ggaacctgtcc tccggccgtt
1441 agcgcgcacg ccgcctcatg tggtcggtcc catcagcgcc gcttccgtt tatagggcc
1501 atgcactgtc actgtggcgaa agtgcgacgac ccgtatggcc gggacggagg cgcgagacc
1561 ggttgcgggc gggccgaac gtggataaa acggggcggtt ggccaggctt gttttttttt
1621 gcaagacgcca ccggccgggaa aaccgtgtt ctattagcca tggcaacccc caccgtgtt
1681 ttgcacattt ccgtcgacgg cgagccctt ggcggcgctt ccgttggggat cggcgccggcc
1741 ggcggcggtt ggaatggggc ccagaaatgg ggcgggggtt ggggtgggtt gtagcgcccc
1801 aaaggccccgg ggcggggggcc accctgttggtggatccccc gggggcgagc gccggccggcc
1861 ttccgtacg agggggccattt tggggaggctt cgcgactgtcc gggaggaggcc cggggacggcc
1921 cggacaaaagg caggcgccggc ggctgtcgagg ccgttgggggg agggggcccg cgtccggcc
1981 cccgcctcat gttggccggcc cttgtccgtt ccgcacgcacg tgctggccgg cccgcgtt
2041 gtccgcgtt tgagactgtt tgccgcctt acgttggccctt gggccggccca gaccggagcc
2101 agaagcacgc tggccggggcc tggcggccac cttccgttggaa agtgcgtcccc tggcggcc
2161 ggggtgtttaa catccgtggac tggaaatgg tttgtgttggatggatccccc aaggatcgat
2221 ggcgggtgtt agcccgatcc tggccgttcc tggatgtcccgatccccc gggaggccat
2281 gagactgttggatgttggatgttggccac tggatgttggatgttggatgttggatgttgg
2341 aatattttata catgtggccccc aaacgtccctt ccgtgtcccccc caccggccaaatgg
2401 aaaatggggcc tggccgttgc tgggtggccaa ggaccggccctt ccactgtcgat gacggccgt
2461 ggcggggagg cgcgttgc tggccgttgc tggccgttgc tggccgttgc
2521 ctggccacaa ggcaggccctt tggccggccaa ggtggattac cttgtgttggatgttggatgtt
2581 ttggagacgtt taaatggatgtt cttaaagatc agtggatgttggatgttggatgttggatgtt
2641 ggcggcggtt tccaaatggatgtt cttaaatggatgttggatgttggatgttggatgttggatgtt
2701 ctttggggatgttggatgttggatgttggatgttggatgttggatgttggatgttggatgttggatgtt

Figure 12. (Page 10 of 33)

Figure 12. (Page 11 of 33)

5821 tgcaaggccc gcctccagg ttcacgccc tctccgtc cagccccc agtagctgg
5881 actataggca catgcccca tgccggcta atttttgc ttttagtag agacagggtt
5941 tcaccgtgtt agccaggatg gtctcgatct cctgaccccg tgatccgccc gcctggccct
6001 cccaaagtgc tgggattaca ggcgtgagcc accgcaccccg gcctataatgt gtaactctt
6061 aatggtaatt ggagaatcat gtttaatgc atttagtaca aaaggctca gttaaaaaaaa
6121 aaaaaaaaaa gctacccccc tcgtctgggt tcatgacaca tggaggctgc ttgttgtgg
6181 ttgccagtc taatgtatgt tctccctttt caagggttgg tggcaagcat gtgggtttt
6241 gcaaagtgaa agaaggcatg aatattgtgg aggccatgg ggcgttggg tccaggaatg
6301 gcaagaccag caagaagatc accattgtg acgtggaca actcaataa gtttgacttg
6361 tgtttatct taaccaccag atcatccctt ctgtagctca ggagagcacc cctccaccc
6421 atttgctcgc agtatccatg aatctttgtg ctctcgctgc agtccctt gggitccatg
6481 ttccctgt tccctccat gcctagctgg attgcagagt taagttatg attatgaaat
6541 aaaaactaaa taacaattgt cctcggttga gttaaatgtt gatgttaggtt ttatTTaaag
6601 cagtaatggg ttacttctga aacatcacctt gttgtctaa ttctacacag tacttagatt
6661 tttttactt tccagcccc ggaagtgtca atgtttgtt agtgaaatat t

protein sequence for Human cyclophilin gene for cyclophilin:

MVNPTVFFDIAVDGEPLGRVSFELFADKVPKTAENFRALSTGEKGFGYKGSCFHRIIPGFMCQGGDFTRHNGTGGKSI
YGEKFEDENFILKHTGPGILSMANAGPNTNGSQFFICTAKTEWLGDGHVVFGKVKEGMNIVEAMERFGSRNGKTSKKI
TIADCGQLE

Figure 12. (Page 12 of 33)M12886. Human T-cell rece...[gi:339009]:

Human T-cell receptor active beta-chain mRNA

DNA sequence:

```
1 gtgtgaggcc atcacggaag atgtgcgtgc ttctgcgtct tctggggcta gcaggctccg
 61 ggcttggcgc tgcgtctca caacatccga gctgggttat ctgttaagagt ggaacctctg
121 tgaagatcgaa gtgcgttcc ctggacttc agggccacaac tatgttttg tatcgtagt
181 tccccaaaca gagtctcatg ctgtatggcaa ctccaatga gggctccaag gccacatacg
241 agcaaggcgt cgagaaggac aagtttctca tcaaccatgc aagcctgacc ttgtccactc
301 tgacagtgc cagtgcctat ccgtaaagaca gcagcttcta catctgcagt gctagagagt
361 cgactagcgt tccaaaaaat gagcagtct tcggggcagg gacacggcgc accgtcttag
421 aggacactgaa aaacgtgttc ccacccgagg tcgcgtgtt tgagccatca gaagcagaga
481 tctcccacac cccaaaaggcc acactgggtt gcctggccac aggcttctac cccgaccacg
541 tggagctgag ctgggggtt aatgggaagg aggtgcacag tggggcagc acagaccgc
601 agccctcaa ggagcagccccc gcccctaattt actccagata ctgcctgagc agccgcctga
661 gggctcggc cacctctgg cagaaccccccc gcaaccactt ccgcgttcaa gtccaggatct
721 acgggccttc ggagaatgac gagttggaccc aggtatgggc caaacctgtt acccagatcg
781 tcagcgccga ggctgggtt agagcagact gtggcttac ctccgagttt taccagcaag
841 gggctcgtt tgccaccatc ctctatgaga tcttgcgtt ggaggccacc ttgtatgccg
901 tgctggtcag tgccctcggtt ctgtatggccaa tggtaagag aaaggatcc agaggctac
961 tccaaaaacca tcccaggta ttcttcatcc tcacccaggta ttcttgcgtt cctgctccca
1021 atctgtgttc ctaaaatgtt ttcttcatctt gcttcttcatc ttcttacttac atgaatactt
1081 ctctttttt tctgtttttt tgaagattttt gctcccc
```

protein sequence:

```
MLL LLL LGLAGSGLGAVV SQHPSW VICKSGTSVKIECRSLDFQATTMF WYRQFPKQSLMLMATSNEGSKATYEQGV
EKDKFLINHASLTLSLTVTS AHPEDSSFYICSA RESTSDPKNEQFFGP GTRLT VLEDLK NVFPPEVA VFEPSEAEISHT
QKATLVCLATGFYPDHWEL SWWVNGKEVHS GVSTD PQLKEQPALNDSRYCLSSRLRV SATFWQNPRNH FRCQVQ
FYGLSENDEWTQDRAKPVT QIVSAEAWGRADCGFTSESYQQGVLSATI LYEILLGKATLYAVLVSALVLMAMVKRKDS
RG
```

Figure 12. (Page 13 of 33)M83664. Human MHC class I...[gi:188478]:

Human MHC class II lymphocyte antigen (HLA-DP) beta chain mRNA

DNA sequence:

1 agcgagtcct tcitttccctg actgcaggcct ttttcattt gccatcccttc tccagctcca
61 tgatggttct gcagggttct gcggcccccc ggacagtggc tctgacggcg ttacgtatgg
121 tgctgctcac atctgtggc caggcggcagg ccactccaga gaattacgtg taccaggc
181 ggcaggaaatg ctacgcgtt aatgggacac agcgcctctt ggagagatac atctacaacc
241 gggaggagta cgcgcgttc gacagcgcacg tgggggagtt ccgggcggtg acggagctgg
301 ggcggcctgc tgccggagttc tggAACAGCC agaaggacat cctggaggag aagcgggc
361 tgccggacag ggtatgcaga cacaactacg agctggacga ggccgtgacc ctgcagc
421 gagtccagcc taaggtaaac gtttccccc ccaagaaggg gcccctgcag caccacaacc
481 tgcttgtctg ccacgtgaca gatttctacc caggcagcat tcaagtccga tggttccctga
541 atggacagga gaaaacagct ggggtcggtt ccaccaacat gatccgtaat ggagactgg
601 cttccagat cctgggtatg ctggaaatga ccccccagca gggagacgta tacatctgcc
661 aagtggagca caccagcctg gacagtccctg tcaccgtggta gtggaggca cagtctgatt
721 ctgcccagag taagacattt acggggagctg ggggcttcgt gctggggctc atcatctgt
781 gagtgggcat cttcatgcac aggaggagca agaaaagtca acgaggatct gcataaac
841 ggttccctgac ctcacccaaa agactaaatg gccttagaac aagcatttgc tgggtttt
901 taacacctgg ttccaggaca gaccctcagc ttcccaagag gatactgtg ccaagaagtt
961 gctctgaagt cagtttctat cgttctgc tttgattcaa agcactgtt ctctactgg
1021 gcctccaacc atgttccctt ctcttagca ccacaaataa tcaaaaccca acataagtgt
1081 ttgccttcctt taaaaatataat gcatcaaatac gtctctcattt acttttctctt gagggttt
1141 gtaaacagta ggagttataa aagaagttca ttttttttca cactgttagaa agaagagaag
1201 catcaaagt gagaataatgtt aactattgtta taatgtggcc ttttatacat gacactcttc
1261 tgaatttact gtatttcactt gactgtcccc caaatcaagt ttatgtccctt catccattt
1321 tgcctcagac cgcttattttttaa aactatttcaaa tggtgagcag actgcaaaatc tgccctgatag
1381 gacccatattt cccacacgac taattcaaca tataatcttac tgagagcatg ttttatcatt
1441 accattaaga agttaaatgaa acatcagaat taaaatcat aaatataatc taataactt
1501 t

protein sequence:

MMVLQVSAAPRTVALTALLMVLTSVVQGRATPENYYQGRQEYAFNGTQRFLERYIYNREEYARFDSDVGEFRAV
TELGRPAAEYWNSQKDILEEKRAVPDRVCRNYELDEAVTLQRRVQPKVNSPSKGPLQHHNLLVCHVTDFYPSI
QVRWFLNGQEETAGVVSTNLIRNGDWTFQILVMLEMTPQQGDVYICQVEHTSLDSPVTVEWKAQSDSAQSKTGT
GGFVLGLIICGVGIFMHRRSKKVQRGSA

Figure 12. (Page 14 of 33)D83779. Human mRNA for KI...[gi:1228040]

Human mRNA for KIAA0195 gene, complete cds

1 cggacatggc tgccgc(ccc) ggaggaggg acgtgaagt aggaggggt tgggagggga
61 gaggacgcgg gcgaggaaga ccagccccgg ggccccatg ttgtactgt gacagactca
121 ctgggttig tacatgc(tgg) ggaggagcct tccttcagg ggtgaccaca ttcatctgg
181 catgcctgca gtactctgg cccatggacc tgaaggagaa gcacctggc gagccctcc
241 cagccctggg cctgtccacg cggaggccc tcagcgltct gaaggagcag ctggaggcag
301 tgcttggaaa acatctcagg gagcggaaa agtgtctgac gtggaaaggag gtgtggagaa
361 gcagcttcct ccaccacagt aaccgctgtc cctgttcca ctggccgggg gcctcactca
421 tgctactggc cggtgtgtc ctgtgggtc gctgccccgg acagccagcc gggagccgt
481 gggggggct ggtgaatgcc tcggccctgt tcctgtact gcttctcaac ctgtgtca
541 tcggccggca agaccggctg aagcgtcggg aggttagagcg gaggctgcga gggatcatt
601 accaaatcca agatgcctc agggatggca gggagatcca gtggccctgt gccatgtatc
661 cagaccccca catgcctttt gcgccttctt ggtccctgca ctggccctac agagacggac
721 acctggtaa cctgcctatc acgcgtgttgg ttgaaggaga catcatagct ttgaggcc
781 gccaggaatc gtttgcgttct ctgagggggta tcaaggatga cgagcacatc gtccctggagc
841 cgggagaccc ctccccccccc ttccccctc caccctcacc cccggggagaa gtggagagag
901 gcccacagag cccccagcag caccggctt tccgtgtct tgagaccctt gtgttgaca
961 acatcagatg gtgcgtggac atggccctgt cccgaccatg cactgcctg gacaatgagc
1021 ggttacatgtt gcatgtgtt atgttacact atgtgtgtc cggtgtctg gccggcttcc
1081 tcatcaccaa tgccctgcgc ttcatctca tgccccggg ggtcaacttcc tggcgttaca
1141 cccctcccca gtcctcaggta aatggcgctc tgcccatctt cccctgcctc ttccctgtcc
1201 tctgggttctt ggcaactgccc tggggagagg cccgtgtctt gccccatgt agcaaggcc
1261 cacccagctc cctgtggct aagtgttca aggtatctt cagcagctat acggaggct
1321 tctcccttc gaaaatgtcg cgctgcattt gggccactt cctgaggggtc ctgggggg
1381 catgcacaaac gtcgtggcc acgttccagcc tgctgcacag cctggctct gtcacgggt
1441 tggctgtgtt ggacaaaacag gggatctgtt catggccaaa tccctggccca gagactgtac
1501 tggcttcag cggaaagggtg gagccccctc acagcggcca tgaggaccc acggatggcc
1561 tatccacccg ctcccttcgcatccggc cccatgaaccc agacgccttc ctggctgg
1621 ccctgaacaa caccctgcac ttcccaatg agcaggagcg tggcacttgc cctggcgagg
1681 ctcccaagcc ccccgagccc tattcacacc acaaagcgc tggccgcagc aaacacccat
1741 ctggcttcaa cgtgagcttc agcaggagaca ccgagggtgg tgaagaagag cccagcaaga
1801 cccagccgg gatggagagc gaccctacg aagcagagga ctgtgtgt gactaccacc
1861 tggagatgtt gggctgtcc caggaccaggc agaacccttc ctgcattccatggatgtact
1921 ccaactggca gtcgcaccc acctccctca aaccctggg cctcaatgtt ctgtgaacc
1981 tgggtgtgc cagcgttacc gggccctgtt gcccatttc cggaccatgt tgcaacatgt
2041 ccctgcacaa gagccacaggc ggcgtgtcc cctggccatgtt gcccggggc ctgtgcgg
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2221 cctgtgtcac caagcgccgg cccatccatgat cggccatctt attaaagaca
2281 ccaccaccatc cacagagcag atgtgttcc atggcaccgc tgatgtggcc tttagaggcc
2341 gcacagactt ctgggacggc gtcgcacatc accctcttc gggatctgtac agaaagaaag
2401 tggacttccatc taccacgcgac ccgtgttgc cttgggtattt ctgtgccttc gcctacaagg
2461 ccataactcg cggccctgtcc tctcgttca atggcaatgtt catcgatgtcg gtacagggt
2521 cccggccaaag cagcatcttc accatgtcg agctgtcccg caccatcccc atcaaggcaga
2581 acggccggcc cagcgttggc agctgtacgc aaggatgttgg ggagggtgtc gagaaggaaag
2641 actgtgttccatc gggccctgtcc gggccatgtt cttgggtttt ggtgtccatc cttgtgt
2701 cccggcttggc catcgatgtcc ctcatgtatg ggctgttcaatc cgcctgcac cgccttgc
2761 acttcttc gggatgttgc ctcaaaaatggc agaaaaaaatggc ggcctggaga

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2821 caggctggaa ctgccacatc tccctcacac ccaatggta catgcctggc tccgagatcc
2881 cccccctccag ccccagccac gcaggctccc tgcatgtga cctgaatcag gtgtcccgag
2941 atgatgcaga agggcttcc tcataggagg aggagggcca ctggacatc atcagctcc
3001 agccatcggc cagcgcacatc cccagcttcc tgaggactc caaccggggcc aagctggccc
3061 ggggtatcca ccaagtgcgg cccccactgc agaacatgta caacgtgccc ctgcttagtgc
3121 ccctttcac cgactgcacc ccagagacca tgtgtgagat gataaaagatc atgcaagatc
3181 acggggaggt gacctgcgtc ctggcagct ctggcaacct gcggAACAGC tgcccttcc
3241 tccagagcga catcagcatt gccctggatc ccctgtaccc atcccggtgc tccctggaga
3301 ccttggcta cggcaccaggc atcagcatgg cccaggccctt ggatggccctt tctccctgc
3361 agctgtcagg gcagctcaac agccctgcctt gttccctgac ctttcggccag gaggagacca
3421 tcagcatcat cccgcatttc gaacaggcgc ggcattccac ctatggcattc cgtaagtgt
3481 tcccttcctt gctcaggatgc cagctgactc ttgtgtcat ccaggcttcc tctggcctgg
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3601 ctctgtcgtc catctctctg ctggggaaagc ccccccatacg ctccatcatg tctatggcaa
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3781 gcttctgtga cagctcccg gaccgcaccc tcaccaactg ctccctggc atgctggcc
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4321 gccagaccca ttctgttgc gggggatgtt tatcatgtat gttccaggat tggcccttgc
4381 accccgtggca ctggaaaccc agctccccgt gtcagaccccc gctgtcttcc tgagccctgg
4441 ggctcactgtt ggaggagatc acggccctgg cccctggccca gtcctggc tccctgggg
4501 ctaccaggac acacttgcata atgtatggcc tcaggcgtc cttttttttt ccctaaaccc
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4681 aacaggcggca gtcctggccca acggcgttcaaa cttttttttt cttttttttt cttttttttt
4741 tggctgtgc ctggatgtgg ccccgagtgc cttttttttt cttttttttt cttttttttt
4801 ccgcctgttgc ctggatgtgg agcaggccccc cccgttgc cttttttttt cttttttttt
4861 tggtgttgc ctggatgtgg ccccgagtgc cttttttttt cttttttttt cttttttttt
4921 ccccaatgtt gggagaatgt tttttttttt tttttttttt tttttttttt
4981 gaatgttgc atgatgttgc tttttttttt tttttttttt tttttttttt

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Protein sequence of Human KIAA0195

MDLKEKHLGEPPSALGLSTRKALSVLKEQLEAVLEGHLRERKKC
LTWKEVWRSSFLHHSNRCSCFHWPAGSLMLLAVLLLGC^{CGG}QPAGSRGVGLVNASAL
FLLLLNLVLIGRQDRLKRREVERRLRGIDQIQDALRDGREIQWPSAMYPDLHMPFA
PSWSLHWAYRDGHVLNPVSLLVEGDIIALRPGQESFASLRGIKDDEHIVLEPGDLFP
PFSPPPSPRGEVERGPQSPQQHRLFRVLETPVIDNIRWCLDMALSRPVTALDNERFTV
QSVMLHYAVPVVLAGFLITNALRFIFAPSAPGVTSWQYTLQLQVNGVLPIPLLPV
VLATACGEARVLAQMSKASPSSLAKFSEDTLSSYTEAVSSQEMLRCIWHFLRV
TSPTLSHSSLLHSLGSVTLCV рdkQGILSWPNPSPETVLFFSGKVEPPHSSHEDLT
DGLSTRSFCHPEPHERDALLAGSLNNTLHLSNEQERGDWPGEAPKPPEPYSHKAHGR
SKHPGSGNSVFSRDTGGEEEPSKTQPGMESDPYEADFVCDYHLEM^LLSQDQQNPS
CIQFDDSNWQLHHTSLKPLGLNVLLNLCDASVTERLCRFSDHLCNIALQESHSAVLPV
HVPWGLCELARLIGFTPGAKELFKQENH^LALYRLPSAETMKETSLGRLSCVTKRRPPL
SHMISLFKDTTTSTEQMLSHGTADVLEACTDFWDGADIYPLSGSDRKKVLDFYQRA
CLSGYCSAFAYKPMNCALSQLNGKIELVQVPGQSSIFTMCELPSTIPKQNARRSS
WSSDEGIGEVLEKEDCMQALSGQIFMGMVSSQYQARLDIVRLIDGLVNACIRFVYFSL
EDELKSKVFAEKMGLETGWNCHISLTPNGDMPGSEIPPSSPSHAGSLHDDLNVSRDD
AEGLLLMEEEGHSDLISFQPTDSIDIPSFLEDSNRAKPRGIHQVRPHLQNIIDNVPLL
PLFTDCTPETMCEMIKIMQEYGEVTCC^LGSANLRNSCLFLQSDISIALDPLYPSRCS
WETFGYATSISMAQASDGLSPLQLSGQLNSLPCSLTFRQEETISIIRLIEQARHATYG
IRKCFLFLLQCQLTLVVIQFLSCLVQLP^{LL}STTDILWLSCFCYPLLSISLLGKPPHS
SIMSMATGKNLQSIPKKTQHYFLLCFLLKFSLTISSCLICFGFTLQSFCDSSRDRNLT
NCSSVMLPSNDDRAPAWFEDFANGLLSAQKLTAALIVLHTVFISITHVHRTKPLWRKS
PLTNLWWAVTVPVVLLGQVVQTAVDLQLWTHRD^HFVHFGLEDVPLLTWLLGCLSLV
VVTNEIVKLHEIRVRVRYQKRQKLQFETKLGMNSPF

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L36719, *Homo sapiens* MAP ...[gi:685173]

Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds

1 tggctggcaa tggcctgtc gaccccgag cgggcccacg tggggaccc tggagcacag
61 cctacatcc tggtgcagg ccgtggatg cagaggccag tccatatacc acccaggcc
121 gcgaggagcg tggccccac ccatccagcc catatgtca agtgccttg acagagaggc
181 tggtcataatc catggtgacc atttatggc cacaacaggc ccccatctgc gcagtgaacc
241 ctgtgtcgag cacccgtcag acgtgtatcc gcttcgtctt gcagactgt gccccggagg
301 aaaatccaag aggaagaagg atctacggat atccgtatc tccaaggccac cccgaccCAA
361 ccccacaccc ccccggaacc tgactcccg gacccatc accattggag acagaaact
421 tgagggtggag gctgtactt tggtgaccat ctccaaactg gcccgtggag cctatgggt
481 ggttagagaag gtgcggcagc cccagagccg caccatcatg gccgtgaagc ggatccggc
541 caccgtgaac tcacaggagc agaaggccgt gctcatggac ctggacatca acatgcgcac
601 ggtcgactgt ttctacactg tcaccatcta cggggacta ttcaagaggg gagacgtgt
661 gatctgtcgagc acacatccctt ggacaaggcc tacccggagg tgctggataa
721 aaacatgaca attcccgagg acatccctgg ggagatgtct gtgtctatcg tgccggccct
781 ggagcatctg cacagcaagc tgccgtatc ccacagagat gtgaaggccct ccaatgtcc
841 tatcaacaag gaggccatg tgaagatgtg tgactttggc atcgtggct acttgggt
901 ctctgtggcc aagacgtatgg atgcggctcg caagccctac atggccctcg agaggatcaa
961 cccagagctg aaccagaagg gctacaatgt caagtccgac gctcgaggcc tgggcacac
1021 catgtatggat atggccatcc tggcgttccc ttacgagltcc tgggggaccc cgttccagca
1081 gctgaagcag gtgtgtggagg agccgtcccc ccagctccca gccgaccgtt tctcccccga
1141 gtttgtggac ttactgtctc agtgcgtcg gaagaacccc gcagagcgta tgagctaccc
1201 ggagctgtatgg gacccatctt tcttcaccc tgcacaaaacc aagaagacgg acatgtctc
1261 ctctgtgaag aagatccctgg gagaagactc ataggggtcg ggcctcgac cccactccgg
1321 ccctccagag ccccacagcc ccatctgcgg gggcagtctc caccacaccataaact
1381 gccatccctgg cccaggccat ctgggaggaa ccggggggcc tgcctccacc tggctctgt
1441 gcgagccatt tgcccaagt gccaaagaag cagaccattg gggctcccg ccaggccct
1501 gtcggcccca ccagtgcctc tccctgcgc tcttaggacc cgttcccgat tgctgagatc
1561 ctggactgtgg gggccctggat tgccccctgt ggtgtctgt gcccctgcac agcaggctgc
1621 cagtgcctgg tggtatgggc caccgccttg ccacgcctgg atgcacatcca agttgtat
1681 ttttttaatc tctcgactgtatggacttgc cacacttgg cccagggtgg ccacaccct
1741 atcccccgtt tggtgcgggg tacacaagag gggatgagtt tggtgaatcc cccaaagact
1801 ccatgaggga gatgccatga gccgcccac gcttccccc ggcactggca aacaggccct
1861 ctgcggagca cactggctca cccagtcgtcg cccgcccaccc ttagccgtgt cattcaccct
1921 tcgtgtttttttat tctctgtatgg tttttcttgc tgcctttaggg tttttggctt
1981 tttttcttgc atgggttggat gctgtatgtatcc tctcccccac ccccttaggggg

Protein sequence of Homo sapiens MAP kinase kinase 3 (MKK3)

MSKPPAPNPTPPRNLDTSRTFITIGDRNFEVEADDLVTISELGGRG
AYGVVEKVRHAQSGTAIMAVKRIRATVNSQEQQKRLMDLDINMRTVDCFYTVTFYGA
REGDVWICMELMDTSLDKFYRKVLDKNMTPEDILGEIAVSIVRALEHLHSKLSVIHR
DVKPSNVLINKEGHVKMCDFGISGYLVDSVAKTMDAGCKPYMAPERINP
ELNQKGYNVKSDVWSL GITMIEMAILRFPYESWGTPFQQLKQVVEEPSPQLPADRF
SPEFVDFTAQC LRKNPAERM SYLELMEHPPFTLHKTKTDIAAFVKKILGEDS

Figure 12. (Page 18 of 33)

U47634. Human beta-tubuli...[gi:1297273]

Human beta-tubulin class III isotype (beta-3) mRNA, complete cds

1 atgcgggaga tcgtgcacat ccaggccgc cagtgcggca accagatcg ggccaagttc
61 tgggaagtca tcagtgtga gcatggcattc gaccccagcg gcaactacgtt gggcactcg
121 gacttgcgc tggagcggat cagcgctac tacaacgagg ccttctca caagtacgtg
181 cctcgagcca ttctgggaa ccttggaaacc ggaaccatgg acagtgtccg cttagggggc
241 ttggacatc tcttcaggcc tgacaatttc atcttggtc agagtgggc cgccaacaac
301 tgggccaagg gtcaactacac ggagggggcg gagctgggtt attcggctctt ggatgtggg
361 cggaaaggagt gtggaaaactg cgactgcctg cagggttcc agctgaccca ctgcgtggg
421 gggggacgg gctccggcat gggcacgtt ctcatacgca aggtgcgtt ggatgttcc
481 gaccgcatca tgaacacattt cagcgctgtt ccctcaccca aggtgtcaga cacgggtgt
541 gaacctata acggccacgtt gttccatccac cagctgggtt aaaacacgga tgaaacctac
601 tgcatacgaca acgaggcgctt ctacgacatc tgctccgc ccctcaagct ggccacgccc
661 acctacgggg acctcaacca cctggtatcg gccaccatga gggagtcac caccccttg
721 cgctcccg gccagctaa cgctgacccgtt cgcaagctgg ccgtcaacat gggtccccctt
781 ccgcgcctgc acttctcat gcccccttc gccccccca ccaggcgggg cagccagcag
841 taccggggcc ttgaccgtgcc cgagctcacc cagcagatgt tcgtatccaa gaacatgt
901 gcccgcgcg accccgcgc gggccgtac ctgacgggtt ccacccgtt ccggggccgc
961 atgtccatga aggagggtt gggccatcc agagaagaa cagcagctac
1021 ttctggatgtt ggatccccaa caacgtgaag gtggccgtgt gtgacatccc gccccggc
1081 ctcaagatgtt cctccacattt catcgggaaac agcaaggccca tccaggagctt gtcaagcgc
1141 atctccgcgc agttcacggc catgttccgg cgcaaggcccttgcactgtt gtacacgggc
1201 gagggcatgg acgagatgg gttcacccggag gccgagagca acatgaacga cctgtgtcc
1261 gagtaccagc agtaccagga cgccacggcc gaggaagagg gcgagatgtt cgaagacgac
1321 gagggaggatgtt cgaggccca gggcccaag tgaaactgtt cgcagctggta gtgagaggca
1381 ggtggccggcc gggggccgaag ccagcgtgtt ctaaaccctt ggagccatctt tgctggccac
1441 accctgtttt ccccatcgcc cttagggctcc ctggccccc tccctgcgtt ttatggctt
1501 cgtccctcccc caccatggcc acgtgtgagc tgctccgtc tctgttctt tgcaagctcca
1561 ggcctgtacgtt ttacgggtt tggttgtgtt ttatattttc ggggatactt
1621 aataaaatcta ttccgttca ataccctt

Protein sequence of Human beta-tubulin class III isotype (beta-3)

MREIVHQAGQCGNQIGAKFWEVISDEHGIDPSGNYVGDSLQL
ERISVYYNEASSHKYVPRAILVDLEPGTMDSVRSGAFGHLFRPDNFIFGQSGAGNNWA
KGHYTEGAELVDSVLDVVRKECENCDCCLQGFQLTHSLGGGTGSGMGTLLISKVREEYP
DRIMNTFSVVPSPKVSDTVVEPYNATLSIHQLVENTDETYCIDNEALYDICFRTLKLA
TPTYGDLNLHVSATMSGVTTSRFPQQLNADLRKLAVNMPFPRLHFFMPGFAPLTRR
GSQQYRALTVPELTQQMFDAKNMMAACDPRHGRYLTVATVFRGRMSMKEVDEQMLAIQ
SKNSSYFVEWIPNNVKAVCDIPPRGLKMSSTFIGNSTAIQELFKRISEQFTAMFRRK
AFLHWYTGEGMDEMEFTEAESNMNDLVSEYQQYQDATAEEEGEMYEDDEEESEAQGPK

Figure 12. (Page 19 of 33)M19267. Human tropomyosin...[gi:339943]

Human tropomyosin mRNA, complete cds

1 cagaatctcc ggcaagtttt gtacctcaag aagtaagtgg aacacccttc cctgtcatag
61 ttatttcat ccagacatct ggtggaagca tcagattct tacagatata agagaggcat
121 catttaaaag gttagaacagg atcgacaac aaggattat gtcaggatct ctccgcctct
181 gtgttaccga gggcattct aacagtcttc ttactacggc ctccgcgcac cgccgcctcg
241 ccccgccgc tctgtgcag ccccaggccc cctcgccgc gccaccatgg acgcaccaa
301 gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag ctgagcaggc
361 ggaggccgac aagaaggccg cggaaagacag gagcaagcag ctgaaagatg agctgggtgc
421 actgaaaaag aaactcaagg gcacccgaaga tgaactggac aaatactctg aggctctaa
481 agatccccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg aagccgacgt
541 agcttcttg aacagacgc tccagctgg tgaggaagag ttggatcgatg cccaggagcg
601 tctggcaaca gcttgcaga agctggagga agctgagaag gcagcagatg agagttag
661 aggcatgaaa glicattgaga gtcgagccca aaaagatgaa gaaaaaaaaatgg aaattcagga
721 gatccaactg aaagaggca aacatgc tgaagatgcc gaccgcaaat atgaagaggt
781 gccccgttaag ctggcatca ttgagagcga cctgaaacgt gcagaggagc gggctgagct
841 ctcaagggc caagtccgac agctgaaaga acaattaaga ataatggatc agaccttcaa
901 agcattaaatg gtcgagagg ataagtactc gcagaaggaa gacagatag aggaagagat
961 caaggccctt tccgacaagc tgaaggaggc tgagactcgg gctgaggttt cggagaggc
1021 agtaactaaa ttggagaaaaa gcattgtga cttagaagag aaagtggctc atgccaaga
1081 agaaaaaccctt agtatgcac agatgctgg tcagacttta ctggagttaa acaacatgt
1141 aaaaaccctt tagtgcac cacattttt cattttttt tgtttttt tgttttaaa
1201 cacctgcta ccccttaaat gcaattttt tacttttacc actgtcacag aaacatccac
1261 aagataccag cttagtcagg ggggtggggaa aacacataca aaaagcaagc ccatgtcagg
1321 ggcgcctgg tccaaatgtg ccattttcccg gtttgatgtt gcccacactt gtagagagg
1381 tagcaacaca gtgtgcctag tcagcgttag aatcctcact aaagcaggag aagtccatt
1441 caaaatgcca atgatagatg caacaaggaa ggttaatgtt gggaaacacaa tcaggtgtgg
1501 attggtgctt cttagaacaa aaggccccctt tggtgttt tttttttttt ttttttttt
1561 agaactctgt ccaacactaa ttatgttctt ctgtttttt actacaagat gagactatgg
1621 atcccgcatg cct

Protein sequence of Human tropomyosin

MDAIKKKMQMLKLDKENALDRAEQAEADKAAEDRSKQLEDELV
SLQKKLKGTEDELDKYSEALKDAQEKLAEKKATDAEADVASLNRRQLVEEELDR
QERLATALQKLEEAKADESERGMKVIESRAQKDEEKMEIQLKEAKHIAEDADR
KYEEVARVLVIIESDLERAEEAELSEGQVRQLEEQLRIMDQTLKALMAEDKYSQKE
DRYEEEIKVLSDKLKEAETRAEFAERSVTKLEKSIDDLEEKVAHAKEENLSMHQMLDQ
TLLELNNM

Figure 12. (Page 20 of 33)

S78798. 1-phosphatidylino...[gi:1042033]

1-phosphatidylinositol-4-phosphate 5-kinase isoform C [human, peripheral blood leukocytes, mRNA, 1835 nt]

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1 ttacacttta tactccggc tcgaataattg tggaaattg tgancggata acaatttcac
61 acaggaaaca nctatgacct tgattacgc aagctcgaaa ttaaccctca ctaaaggaa
121 caaaagctgg agctcgccgc cctgcaggc gacactagt gatcaaaga attccgcacg
181 aggccacggg cggagcggag cgccggccgc cggggccgccc gcggggggga tcggctgcct
241 ccccgcccg ggttagaga gggcggtcc cggccctcg gggcacggcg gtggagggga
301 cataggaggc gcgcattggcg accccccggca accttagggtc ctccgtcccg gcgagcaaga
361 ccaagaccaa gaagaagcac ttcttagcgc agaaagt gatgtttcg gccaacgcacc
421 cgcgtctcg cgtcttcatg tggggggtaa accactcgat caatgaactg agccatgttcc
481 aaatccctgt tatgttgatg ccagatgact tcaaagccta ttcaaaaata aagggtggaca
541 atcaccttt taacaaagaa aacatgccga gccatttcaa gtttaaggaa tactgcccga
601 tggcttcgg taactgcggg aagaggttt gatgttgc tcaagatttc cagaattccc
661 tgaccaggag cgccacccctc cccaaacgact cccaggcccg cagtgagct cgtttcaca
721 ctccctacga caaaagatac atgatcaaga ctattaccag tgaagacgtg gccgaaatgc
781 acaacacatctt gaagaaatac caccatcata tagtggaaatg tcatggatc acccttc
841 cccacttgtt gggcatgtac cggcttaatg ttatggatg tggaaatataat gtatgttta
901 caagaaatgtt attcggccac cggttgcgtg ttataggaa atacgactta aagggtctta
961 cagtggctag agaagctgtt gacaaagaaaa aggccaaaga actgccaact ctggaaagata
1021 atgatttcat taatggggc caaaagattt atattgtga caacagcaag aagggtttcc
1081 tggaaaaact aaaaaaggat ttatggatg tggccctgtt gaacttcatg gactacatc
1141 tgcgttggg aattcatgtat gggagagag cggaaacagga ggaagtggag tggaggaga
1201 acgtgggggaa ggaggagggc gagaggcatg gcacccaccc gttggaaacc ccccgagata
1261 gccccggaa tacactgaac agtcaccac ccctggctcc cggggagttc gagccgaaca
1321 tcgacgtcta tggaaattaag tgccatgaaa actcgcttag gaaggagggt tacttcatgg
1381 caattattgtt catccatctt cattatgtat caaaaaaaaa agctgcccattt gctgcaaaaa
1441 ctgttaaaca tggcgctggc gggagatctt ccacccgttac cccagaacag tattcaaaagc
1501 gcttttggaa cttatggc cacatcttgc cgttccatc tggccaytc ggacagcatg
1561 aacattggat ggacagaggtt ggctcggtt tagaaaaat gaaaacccaaat ctcgtgaag
1621 tactcatctt gcaggaagca aaccccttgc ttatcatctt caggccaaaga tgactgtt
1681 gggggctact cgcttacag ctacctgtt ttccctgtt cgttctgtt atttctgtact
1741 ttgtgttatg ttgtgtgtt ttgtgtggg ggggggtttagt ttgtgtccg cttttttttt
1801 taaagcataaa attaattaaa cagccacttc ggtca

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Protein sequence of 1-phosphatidylinositol-4-phosphate 5-kinase isoform C

```

MATPGNLGSSVLASKTKKKHFVAQKVKLFRASDPLLSVLMWG
VNHSINELSHVQIPVMLMPDDFKAYSKIKVDNHLFNKENMPSPHFKFKEYCPMVFRNCG
KRFGIDVQDFQNSLTRSAPLPNDSQARSGARFHTSYDKRYMIKTITSEDVAEMHNILK
KYHQYIVECHGITLLPHLLGMYRLNVDGVEIYIVTRNVFSHRLSVRKYDLKGSTVA
REASDKEAKEPTLKDNDFINEGQKIVIDDNSKKVFLEKLKDVEFLAQKLMDYSL
LVGIHDVERAEQEEVECEENDGEEEGESDGTHPVGTPPDSPGNTLNSSPPLAPGEFEP
NIDVYGIKCHENSPRKEVYFMAIIDILTHYDAKKAAHAAKTVKHGAGAEISTVNPEQ
YSKRFLDFIGHILT

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Figure 12. (Page 21 of 33)

X58851. Human MLC1emb gen...[gi:34680]

Human MLC1emb gene for embryonic myosin alkaline light chain, promoter and exon 1

Protein sequence of Human MLC1emb gene for embryonic myosin alkaline light chain, promoter and exon 1
MAPKKPEPKKEAAKPAAPAPAPAPAPAPAPEAPKEAFDPKSV
KIDFTADQIEEFKEAFSLFDRTPTGEMKITYGQCGDVLRALGQNPTNAEVLRLVGKPK
PEEMNVVKMLDFETFLPILQHISRNEQGTYEDFVEGLRVFDKESNGTVMGAELRHVLA
TI GEKMTFAEVFVEQQLLAGQFDANGCINYFAEVKHIIMSG

Figure 12. (Page 22 of 33)

X90999. H.sapiens mRNA fo...[gi:1237212]

H.sapiens mRNA for Glyoxalase II

Protein sequence of H.sapiens mRNA for Glyoxalase II

MKVEVLPA TDNYMLVIDDETKEAAIVDPVQPQKVVDAA RKG
VKLTTVLTTHHWDHAGGNEKLVKLESGLKVYGGDDRIGAL THKITHLSTLQVGSLNV
KCLATPCHTSGHIC YFVSKPGGSEPPAVFTGDTLFVAGCGKFYEGTADEMCKALLEVL
GRLPPDTRVYCGHEYTINNLKFARHV EPGNAIREKLA WAKEKYSIGEPTVPSTLAAE
FTYNPFPMRVREKTVQQHAGETDPVTMRAVRREKDQFKMPRD

Figure 12. (Page 23 of 33)

AF027515. Homo sapiens tran...[gi:2772909]

Homo sapiens trans-golgi network glycoprotein 48 (TGN) mRNA

1 agaggggccc cgccgcgaga ttcgcgaga gcattagagg gcggaagcgc tatccgagca
61 ggtgcggtt cgtgggtgcc ttggcttcc tgaacgtcg acggcgaaa gccgtccgc
121 tctggccac cgaagcgctc aagcaagaag aagctggagt acggcccttc gcagaaacg
181 tctccacca ccccaagctt agccaacggc ctggaggctc taccatcg catccggagc
241 cgcagactcc aaaagacagc cctagcaagt cgagtgcggg ggcgcagacc ccagaagaca
301 ccccccaacaa gtgggtggg gaggcaaaga ccctaaaaga cagctccaac aagtccggtg
361 cggaggcaca gacccccaaa ggcagacta gcaagtccggg ttccggaggcg cagaccacaa
421 aagacagcac tagtaagtcg catccggagc tgcatcgactcc aaaagacagc actggccaaat
481 cgggtgcggg ggcgcagacc ccagaagaca gccccaaacag gtccgggtcg gaggccaaaga
541 cccaaaaaga cagccctagc aagtccagggtt cggaggcgca gaccacaaaa gatgtcccta
601 ataagtccggg tgccgcggc cagaccccaa aagacggctc cagcaagtgc ggtgcggagg
661 atcagacccc aaaagacgctc ctaacaagt cgggtgcggg gaagcagact cccaaagacg
721 gctctaacaa gtccggtgca gaggaggcagg gccaaataga cggggccacg aagtccggtg
781 cggaggagca gacctaaaaa gacagccctaa acaagggtt tccagagcag ccttcccgga
841 aagaccatlc caagccatc tccaaccctt ctataacaa ggactcccc aaggctgaca
901 caaacccatc tgctgacaaa gggaaagctt ccctcatcg ttccaaacc gaatctgggg
961 aggaaactgatc cctccatctt ccccccgcagg aggaagttaa gtctcagag cctactgagg
1021 atgtggggcc caaagaggct gaagatgtatc atacaggacc cgaggaggc tcacccccc
1081 aagaagagaa agaaaaagatc tccgggtctg cttccatcgta gaaccgtgaa gggacactt
1141 cggatccac gggtagcgag aaggatgacc ttatccgaa cgggtctggaa aatggcagcg
1201 cggagagcag ccacttcattt gcataatcgatc tgactgcagc cattcttgtg gctgtccct
1261 atatcgctca tcacaacaag cggaaagatca ttgcattttt cttccatcgaa aaaaagatcta
1321 aagtccatccg gcccggccaaag gcccactgact accaacgtt ggaccagaag atcttttc
1381 ccccaagtc taacagaatgt gtatattctt ctggaaaaaaatgtaaactgca ccaatggatt
1441 gtgtcgctc cgatccatcgatc ttgtttttt tgccatcgatc aaccatcgatc tccctgtca
1501 ttgttttcta aatcaaaaaga aatgaagaaaa aaagtactgt gacccatcgatc acaccct
1561 ctggaaattttta gtggccggc tgggtcgatc gaggttagggg gctgttttttgcgttgcacc
1621 tgacatccatcgatc ttgtttttt tgccatcgatc aaccatcgatc tccctgtca
1681 ttccatcgatc ggggtggatc aggggttatc gggaaacacgg cttatcgatc aaggatcc
1741 cggccatcccg gggatccatcgatc gggatccatcgatc cttatcgatc aaccatcgatc
1801 tggccatcgatc ctgtggatccatcgatc ctgtggatccatcgatc aaccatcgatc
1861 tggccatcgatc aaccatcgatc aaccatcgatc aaccatcgatc
1921 agacatagaa aatggggaaaaa tgccatcgatc aaccatcgatc
1981 tccaaatcgatc aaccatcgatc aaccatcgatc
2041 caaccatcgatc aaccatcgatc
2101 gacaaaatcgatc aaccatcgatc
2161 gggccatcgatc aaccatcgatc
2221 atccatcgatc

Protein sequence of Homo sapiens trans-golgi network glycoprotein 48 (TGN)

MRFVVALVLLNVAAGAVPLATESVKQEEAGVRPSAGNVSTHP
SLSQRPGGSTKSHPEPQTPKDSPSKSSAEAQTPEDTPNKGGEAKTLKDSSNKSGAEAE
QTPKGSTSCKGSEAQTTKDSTSCKSHPELQTPKDSTGKGAAEATQPEDSPNRSGAEPKT
QKDSPSKSGSEAQTTKDVPNKGADGQTPKDGSSTKSGAEQDQTPKDVPNKGAEKQTPK
DGSNKSGAEEQGPIDGPSKSGAAEQTSKDKSPNKKVPEQPSRKDHSKPISNPSDNKELP
KADTNQLADKGKLSPHAKTESGEETDLISPPQEEVKSSEPTEDVGPKAEEDDTGPE
EGSPPKEEKEKMSGSASSENREGTLSSTGSEKDDLYPNGSGNGSAESSHFFAYLVTA
AILVAVLYIAHHNKRKIIAFVLEGKRSKVTRRPKASDYQRLDQKIFSPPSPNRMVYSS
GKR

Figure 12. (Page 24 of 33)AJ223352. Homo sapiens mRNA...[gi:3255996]**Homo sapiens mRNA for histone H2B**

1 gccgtcgcc ttcaacatgc cggAACCGAGC gaagtccgt cccgcGCCCA agaagggctc
61 gaagaaaAGCC gtgactaagg cgCAGAAAGAA ggacggtaa aagcgcaAGC gcagCCGCAA
121 ggAGAGCTAC tccgtatacg tgtacaagggt gctgaAGCAG gtccACCCCG acaccGGCAT
181 ctccTCTAAG gccATGGGAAC tcatGAACtC cttcgtaaac gacatTTG aacgcATCGC
241 gggTgAgGCT tcccgctgg cgCATTACAA caAGCgCTG ACCATCACCT ccAGGGAGAT
301 ccAGACGGCC gtgcGCCtGC tgctGCCGG ggAGTggCC aAGCACGCCG tgCCGAGGG
361 cACCAAGGCC gTCACCAAGT ACACCAGCGC TAAGTAACt tgccaaggAG ggACTTCTC
421 tggAAATTCC tGATATGACC aAGAAAGCTT CTTATCAAA GAAGCACAAT tgccTCCGT
481 tacCTCATTa tCTACTGCG aAAAGAAAGAC gagaATGCA ccatacCTAG atggACTTT
541 ccACAAGCTA aAGCTGGCTT CTTGATCTCA ttcAGATTCC AAAGAGAAATC ATTACAAGT
601 taATTCTGT CTCCtGGtC CATTCCTCT CTTATAAT CATTACTGT TCCtCAAAGA
661 atGTTTACA tTACCCATCT CCTCTTtGtC tCTGAGAAAAG AGtATAAG CTTCTGtAcc
721 ccACTGGGGG GTTGGGGtaA tattCTGtGG tCCtCAGCCC TGTACCTAA taaATTtGta
781 tGCCtTTTT ttaaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa

Protein sequence of human histone H2B

MPEPAKSAPAPKKGSKKAVTKAQKKDGKKRKRSRKESYSVYVYK
VLKQVHPDTGISSKAMGIMNSFVNDFERIAGEASRLAHYNKRTITSREIQTAVRLL
LPGEAKHAVSEGTKAVTKYTSAK

Figure 12. (Page 25 of 33)L42542. Human RLIP76 prot...[gi:974142]**Human RLIP76 protein mRNA, complete cds**

1 agtctggttt aactggttgg aacgactaaa gcacgcgtggc gcaaggaaag ctctcaactt
61 cgggagctga ggcgcaggct ggccagagcg tggagaggaa agcccttcc atcctaagg
121 ccgttgaggc agatgcccgc gagccacatt cggcagacc acaccgggtt gtaatggata
181 ggttaacagag aagacctcg tcccttc tagggcattc agcatactg agtgcttcc
241 gccccccacc accgagccccca gtgaacacccg cagggtggag catggcagcg ggcttacccg
301 gaccccccagc tctgaagaga tcagccctac taagtttcc ttgattgtacc gcactggcg
361 gcccctcaccc cccatgaca tcccttcatga gccttcgtat gtatgtctg atgttagagaa
421 agatcatggg aagaaaaaaag gggaaattttaa gaaaaaggaa aagaggactg aaggctatgc
481 agcctttcag gaagatagct ctggagatga ggcagaaagt ctttctaaaa tgaagaggtc
541 caagggaaatc catgtttca agaagcccag ctttctaaaa aagaaggaaa aggattttaa
601 aataaaaagag aaacccaaag aaaaaaagca taaaagaagaa aagcacaag aaaaaaaaca
661 taaagagaag aagtccaaag acttgacacg agctgtatgtt gttaaacagt ggaaggaaaa
721 gaagaaaaaaag aaaaagccaa ttctaggagcc agagggtcct cagattgtatg ttccaaatct
781 caaacccatt ttggaaattt cttggctgtc tgcatgtatgg aggaccatgt tgatgtatgg
841 cattcggtcg ccagccgtt tccgtgtatg tataattttc gtatgtatgg atggcatgaa
901 gtgtgaaggc atctacagag tatcaggaat taaaatcaaag gtggatgagc taaaagcagc
961 ctatgaccgg gaggagtcta caaacttggaa agactatgtt cctaactgt tagccatgtt
1021 gctgaagcag tatttgcgag accttccaga gaatttgcgtt accaaagagc ttatgcccag
1081 atttgaagag gcttgcgggaa ggaccacccgaa gactgagaaaa gtgcaggat tccagcggtt
1141 actccaaagaa ctggcagaat gtaactatct tctgttttct tggcgttccatgg
1201 ccatgtcattt gcaaaaggaaac tggaaacaaa aatgtatata cagaacatattt ctatgtgt
1261 cagcccaactt gtgcagatca gcaatcgagt cctgtatgtt ttttcacac atgtcaaga
1321 actcttttgcgaa aatgtgttac taaagcaagt gtgaaacccctt ctgcgttccatgg
1381 cacgtgccc acgctgccag agacccaggc gggcatcaag gaggatgtca ggagacaggg
1441 gtttcttttgcgaa aatgttttac atcgagatctt gcagggtggg ataaaggattt ttttctaaaga
1501 agaaaagatgtt tggaaagtac aaaaatttt gacagccctc aaaagaaaac tgagagaagc
1561 taaaagacag gagtgcgttccatggaa ccaagattgc acaagagata gccaatgtt caaaagagga
1621 tttttccaaa gaagatgtatgtt aaaaatgtt aatatttctt ttttcttccatgg
1681 gaatgtatgttccatggaa ctttttttttccatggaa ctttttttttccatggaa
1741 gattgcctca gaaaaaaag agattgtatgtt ctttcgtatgtt aatattcagatgt
1801 tcggccatgtc ctttttttttccatggaa ctttttttttccatggaa
1861 tgaggatgtatgttccatggaa ctttttttttccatggaa
1921 gggaaatataatgtatgttccatggaa ctttttttttccatggaa
1981 gctgcgcgtt ctttttttttccatggaa ctttttttttccatggaa
2041 ggaggacggag gggccgttccatggaa ctttttttttccatggaa
2101 tgaggatgtatgttccatggaa ctttttttttccatggaa
2161 ctttttttttccatggaa ctttttttttccatggaa
2221 agactgaaatgtatgttccatggaa ctttttttttccatggaa
2281 acatcttcgttccatggaa ctttttttttccatggaa
2341 cacgtcaggc ttttttttttccatggaa ctttttttttccatggaa
2401 ctttttttttccatggaa ctttttttttccatggaa
2461 aataactatgtatgttccatggaa ctttttttttccatggaa
2521 ttttttttttccatggaa ctttttttttccatggaa
2581 ctttttttttccatggaa ctttttttttccatggaa
2641 ttttttttttccatggaa ctttttttttccatggaa
2701 ttttttttttccatggaa ctttttttttccatggaa
2761 gtttttttttccatggaa ctttttttttccatggaa
2821 aggggttttttccatggaa ctttttttttccatggaa

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2881 cggcccgltc ctgcacgttc ctcaactgcgg ggaccagcaa aggccitcic actgggttgg
2941 tcaaaggtag tcaccctggc ctggtgcatc cacagaggat gttgtcaaa ccagaaatct
3001 tttaaacgac tgaccctcct taaaaacaga atgactccga ttgcttgctt ggcttagaat
3061 gtacacgtct cttgcctga ataagccata tatatgtct taaacaaaag ttgaaattta
3121 tccataatcat ctcagtgaac ctactggtg actcccaatt gacaagattt agcaatagaa
3181 aaaaattcct ttccittgaa ttagatgtt gattcaccccc accccattti ctgtttctg
3241 gtccatccga tgagacggat gctctgtatgc tlgaggctt ctggggggctt gggccctgga
3301 ggcaacgtgc tgcaaggcga ctctgtcaga gtgaacagca ccgcgagaca ggccaggctc
3361 gtggctcggaa agacaaaccc cacacacact caaggggtcg aaaacaaacc ccacacgagg
3421 gctctcacct cctctccata ggttagtattt attttcagca cctgtttgtat gcagttttt
3481 atcctctacc tattgcactg ttgtgactcg ttggccatta ttgattttt gtacgaaaaaa
3541 aagcttggat atagaatca gcatactattt ttttaatc ttggagagaag atattctgg
3601 gactgaaagt atggcgggt gtcagatata aatgtcaaa tgccttctg ctgcctgtc
3661 ggtctcgtat cgttacttt atagctgcgt gcaatatcga aggttccctt ttgtttgt
3721 taaactctaa ttctatcaa ggtgtatgg attttaaaa tttagtatttcc attacaaatgg
3781 tctcagcatt ggttaactaa ttggcag gaccattt gatcaagcaa ataaattcaa
3841 cagccatttg gggaaaaag

Protein sequence of Human RLIP76

MTECFLPPPTSSPSEHRRVEHGSGLTRTPSSEEISPTKFPGLYRT
GEPSPPHDILHEPPDVVSDDKDGHKKKGFKKKKEKRTEGYAAFQEDSSGDEAESPSK
MKRSKGIVFVKKPSFSKKKEKDFKIKEKPKEEKHKEEKHKEKKSKDLTAADV
KQWKEKKKKKKPIQEPEVPQIDVPLNKPIFGIPLADAVERTMMYDGIRLPAVFRECID
YVEKYGMKCEGIYRVSGIKSKVDELKAAYDREESTNLEDYEPNTVASLLKQYLRLDPE
NLLTKELMRPRFEEACGRTTETEKVQEFQRLLKELPECNYLLISWLIVHMDHVIKELE
TKMNIQNISIVLSPTVQISNRVLYVFFTHVQELFGNVVLKQVMKPLRWSNMATMPTLP
ETQAGIKEEIRRQEFLNLCLHRDLQGGIKDLSKEERLWEVQRILTALKRKLREAKRQE
CETKIAQEIASLSKEDVSKEEMNEEVINILLAQENEILTEQEELLAMEQFLRRQIA
SEKEEIERLRAEIAEIQRQQHGRSETEEYSSESESSEDEEELOQIILEDLQRQNEEL
EIKNNHLNQAIEEREAIIELRVQLRLLQMQRAKAEQQAQEDEEPEWRGGAVQPPRDG
VLEPKAAKEQPKAGKEPAKPSPSRDRKETS

Figure 12. (Page 27 of 33)W26677_11f7_Human retina...[gi:1305788]

TNNNNNTNNNNNTNNCCTGCTCAGCATTGGNTNTGATGTGCTGGTGGAGAACACAG
AAGAATGNATTGCTGAGGGGAGACCTGGTCCAGGGTCTTCCTCCCCTGTAATCCAGGGCCA
CACTGATGAGNTCTGGGGNCTGCACACACCCCTCCCAGAACCGNTTCCTCACCTGCAG
CCACGACCGGNAGTTCTGCCTGTGGATGGGAGAGCCATGCACTGCCCTGGAGCATCGA
CCTCAAGGAGACTGGTCTGTGCTGACTTCCACCCGAGTGGGCAGTTGTGGCGNAGG
ACTGAACACGGGAGGGTGGTTGGTTGGNCACAGAGACCAGAGAGATCGTGTGATGT
CATTGATGGCAATNAGCAGCTCAGTGGTCCGGTACAGNCCAGATGGGTTGGCCTGGC
CCAATTGGTCCCCATNACAACNTNATNTTCAATCTTTNGNGGTTCCAGGGGATGGTG
CCCAATTCCAGNCCNTTTGGGCCNTTGTNTTGGTCAACNCCCAGNTTCAACCACTC
AATNTTGGAGTAGGTTCAANNNTNGNNTTACCAAGTTGNNTNTCCAANNNNNNNNNN
NNTNTNNNTNNTTNTTCTTTNCNTNANNCCNNNNNNNNCNNNTCTNCNTNTNNTC
AANCCNNNTNNNNNNNCNNCNNNNCNTNNCTNCNTNNNNCNNTNNNTNNNN
CNNNNNCTNNNNNTNNNCNNNNNNNN

Protein sequence of Human retina cDNA

No Protein sequence available from GenBank

Figure 12. (Page 28 of 33)X51804. Human PMI gene fo...[gi:35534]**Human PMI gene for a putative receptor protein**

1 ggccccccccc ccccctagaa atgcgtgaac caggacggct cctggagtcc tcggccctc
61 gcagaaggac tacgggcccc ggcgaccccg ggggcggggc ttccggcgcg ctgccttgt
121 ggcacggtag ttccggccgg tctggcttc gcctgcccag cggcccccga ccgcaggccg
181 gactacactt cccgtggcc cccctgcctc cccgtatggcc ccttggcgcg agacgttggc
241 aagcagagtg tctccaagat ggcgcgtgg ggaaggaggc gtctggccc gggcagcagt
301 ggcggcagcg cccgagagag ggtgagctg tcggccacag actgctacat tgtcatgag
361 atctacaatg gggagaatgc ccaagaccag ttgagttacg agctggagca ggcctggaa
421 gcccagtaca agtacattgt gattggagccc actcgcatgg cgcacgagac agcccgctgg
481 atcacccgtgg gcaactgcct gcacaagacg gccgtgtgg cgggcaccgc ctgccttc
541 accccgttgg cgctgccctt agattattcc cactacattt cccgtggccgc tggtgtgt
601 agccggcct gctgcacccct ctatggatc tccctggcagt ttgacccttg ctgcaagttac
661 caaggaggat acgacgccta taaacgtcg cgcctggcc tgcacacact caccctcc
721 accccgggtgg tgctggtccg gaaggacgac ctgcacagaa agagactgca caacacgata
781 gcactggccg ccctgggtta ctgtgtaaag aagatttacg aactctatgc cgtatgattt
841 cagtagaaaca gggagcgaag caaaaccacc cggcccacaa gagacaacag agtattcaga
901 tcgccccact ctgtgaggca gcagacgtcg ggcagggtt tggcttagta ttgttattt
961 taaaaaaaata acagatcacg ggtgtaccca ggggttttca gtcattaca ctaagatgt
1021 gattccata acccaagagg ggggtctgag gctgtggaaag tccgactggg cagtgaaatg
1081 ctgatggagg cagacgcgtgc cgaggggggtg tggacgtgt ttgggggagg tcttaagt
1141 tatttttaa ctgttaccatc cagagccac cagaagctat tgatcattaa aattatgaga
1201 atttcaactc c

Protein sequence of Human PMI

MAAWGRRRLGPSSGGSSARERVSLSATDCYIVHEIYNGENAQDQ
FEYELEQALEAQKYKYIVIEPTRIGDETARWITVGNCLHKTAVLAGTACLTPLALPLD
YSHYISLPAGVVLSLACCTLYGISWQFDPCCKYQVEYDAYKLSRLPLHTLTSSTPVVVLV
RKDDLHRKRLHNTIALAALVYCVKKIYELYAV

Figure 12. (Page 29 of 33)

M24069. Human DNA-binding...[gi:181483]

Human DNA-binding protein A (dbpA) gene, 3' end

1 gaattccgggc gggggagccc aaggagc gag cgccca gac gaagctcgag ccgc cccgc
61 cagcgcgacc ccacctcgcc cgccggcc tccgccccgg cctccccgg
121 agcgagcccc ggccgccc accaccagcc gcgtaaccg ccgaccaacc gccaccgagg
181 cgccctgagcg agagcagagg aggaggaggc atgagtggg cggggcggg caccaccacc
241 accaccacca ccctcccgca ggctccgacg gaggcggccg ccgcggctcc ccaggacccc
301 ggc cccaaaga gcccgggtgg cagcgggtgcg ccccaggccg cggcccccggc gcccggcc
361 cacgtcgac gaaaccccg tggggacgcg gccccgtc acacggcac cgcggccgc
421 gcctctttag ccgcgcgcg cggcagcga aacccggaga aaaaatgtt cgcacccaaa
481 gtccttggca ctgtcaaaatgttcaacgtc agaaaatggat atggattttt aaatcgaaaat
541 gacaccaaag aagatgttatt tgatcatcg actgcacatca agaagaataaa cccacggaaa
601 tatctcgca gtgttaggaga tggagaaact gttagatgtt atgttgttga aggagagaag
661 ggtgcagaag ctgccaatgt gactggcccg gatggagttc ctgtggaaagg gagtcgttac
721 gctgcagatc ggcgcgcgtt a cagacgtggc tactatggaa ggcgcgtgg ccctccccgg
781 aattacgtcg gggaggagga ggaggaagg a cgcgcagca gtgaaggatt tgacccccc
841 gcccacgtata ggcacgttcc ttggggcccg aatcgtcg gcccggccca gtatcgccct
901 cagtacccgc agcggcggtt cccgccttac cactgtggac agacccgttga ccgtcgctca
961 cgggttccat cccatccaa cagaatacag gctggtgaga ttggagagat gaaggatgg
1021 gtcccgagg gaccaact tcaggacccg gtccatcgaa atccacta cgcggccaaagg
1081 taccgttagca ggggacccctcc tccggccacga cctggcccgag cagttggaga ggctgaagat
1141 aaagaaaaatc agcaagccac cagtggtcca aaccagccgt ctgtcgccg tggataccgg
1201 cgtcccttaca attacccgcg tccggcccg tcccttaca cgtcccttac aagatggcaa
1261 agaggccaa g cagggtgaag caccacatga aaccctgtt ccacccaccc agcagagcag
1321 tgtgatgttac accaggctcc tcaggccatcc tccatcggtt cagggtggacc taaagaatta
1381 gatgaccatt cagaataaaa gaaaaaagca ggcacatc cttaccaac accaaagaaa
1441 catccaagca ataaatggg a gactaacc a agatggac atggatgtt atgttgtt
1501 tctttaagaa acaactacaa aaagaaaaatg tcaacaaatt ttccagca gctgagaacc
1561 tggaaattc

Protein Sequence of Human DNA-binding protein A (dbpA)

EFGRGSPRSERARRSSRLQRDPSTAAGLRREIRPGLPESEPR
PPRPPAALTADQPPPRLSESRGGGMSEAGEATTTTTLQPAPTEAAAAAPQDPAP
KSPVGSGAPQAAAPAPAHHVAGNPGGDAAPAATGTAAAASLAAAAGSEDAEKVLATK
VLGTVKWFNVRNGYGFINRNDTKEDVFVHQTAIKKNPRKYLSVGDGETVEFDVVEG
EKGAEANVTGPDPGVPEGSRYAADRRRYRRGYYGRRRGPPRNYAGEEEEEEGSGSSEG
FDPPATDRQFSGARNQLRRPQYRPQYRQRRFPPYHVGQTDFRRSRVLPHPNRIQAGEI
GEMKDGVPEGAQQLQGPVHRNPTYRPRYRSRGPPRPRPAPAVGEAEDKENQQATSGPNQ
PSVRRGYRPPYNYRRRPPSS

Figure 12. (Page 30 of 33)NM_002218. Homo sapiens inte...[gi:4504784]:

Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITIH4)

DNA sequence:

1 gtgagaagcc tcctggcaga cactggagcc acgtgaaggccccaaaggcc tgcgtacc
61 tgcagcaaaat ttctcgctt gccttcactg ctggccatcc accagaccac tactgccgaa
121 aagaatggca tcgacatcta cagcctcacc gtggactcca gggcttcaccccgattgcc
181 cacacggctcg tcaccagccg agtggtaat agggccaata cggtagcggg ggcacccctc
241 cagatggagc tgcccaagaa agccttcacca accaacttct ccatgaacat cgtggcatg
301 acctacccag ggatcatcaa ggagaaggct gaagcccagg cacagtacag cgccggcgt
361 gccaaggaa agaacgcggc cctcgtaag gcccacccggaa gaaacatggc gcaatccatgg
421 gtgtcggtca gtgtggctcc caatgccaag atcaccttg agctggctta tgaggagctg
481 ctcaagccgc gtgtgggggt gtacgagctg ctgctgaaag tgccggccca gcagctggc
541 aagcacctgc agatggacat tcacatctc gagcccccagg gcatcagctt tctggagaca
601 gagagcacct tcatgaccaa ccagctggta gacgcctca ccacccggca gaataagacc
661 aaggctcaca tccggtaaa gccaacactt tccctggcggc aaaagtcccc agagcagcaa
721 gaaacagtcc tggacggcaa cctcattatc cgctatgttg tggaccgggcatctccggg
781 ggctccatc agatcgagaa cggctactttt gtacactact ttggccggaa gggcttaacc
841 acaatggccca agaatgtggt ctgtgttcaat gacaagagcg gctccatgatggcaggaaaa
901 atccagcaga cccggaaagc ctaatcaag atccctggatg acctcagccca cagagaccag
961 ttcaacatca tcgtcttcag tacagaagca actcgtggc ggccatcaact ggtggccagcc
1021 tcagccgaga acgtgaacaa ggcaggagc ttgtcgccg gcatccaggccctgggggg
1081 accaacatca atgtgcaat gctgtggct gtgcagttgc tggacagcag caaccaggag
1141 gagccggctgc cccaaaggag tgcgtactc atcatccctgc tcaccgtgg cgaccccaact
1201 gtgggggaga ctaacccag gagcatccag aataacgtgc gggaaagctgt aagtggccgg
1261 tacagccatct tcgtcggtttc gacgtcagct atgccttcct ggagaagctg
1321 gcactggaca atggccgcct gggccggcgc atccatgagg actcagactc tgccctgcag
1381 ctccaggact tcaccaggaa agtggccaaac ccactgtca cagcgtgac ctccgagatc
1441 ccaagcaatg cccggggaaa ggtcactca gaaacttcc ggctccctt caaggccatc
1501 gagatggtg tggctggaa gctccaggac cggggccctg atgtgtcac agccacagtc
1561 agtgggaagc tgcctacaca gaacatcaat tccaaacgg agtccctgtgt ggcagagcag
1621 gaggccggat tccagagccca caagtatatc ttccacaact tcatggagag gctctggca
1681 tacccgtacta tcaccggact gctggggaa actgtctccg catccgacgc tgatcagcag
1741 gcctccggaa accaagcgct gaatttatca ctggctaca gcttgtcac gcctctcaca
1801 tctatggtag tcaccaaacc ccatgaccaa gagcgttca aagtgtca gaaaggccatg
1861 gaaggccaaa gtagaaacag gaatgtccac tcagggttca ctttcttcaaa atattatctc
1921 caggggacaa aaataccaaa accagggacttcccttccca caagaagagg atggaaataga
1981 caagctggggat ctgtcggttc cccggatgaaat ttccggatgttgc ggggtctcg ctccaggccaa
2041 ctggactcc caggacccctc tgatgttcc gaccatgttc ctaccaccc ctccggcgt
2101 ctggccatct tcgtcggttc agcaccacca gccacccaaatccatgttc agctgtgt
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2221 caggctccct tcgtcggttc gccactgcct gggcggatgt tggagccgt ctgtgtggac
2281 cccagacacc gccaggggcc agtggacccctg ctctcggacc ctggaccaagg ggttggggat
2341 actggccatg atgagaggaa gaaggctggg ttctcatgttca tcggatgtac ctcaagaac
2401 cccctggat ggggttcacgc atcccttcaaa cacgtggatgt tgactcgaa ccgaagaagc
2461 tctgtgtaca agtggaaagga gacgttccatc tcgtgtatgc cccggccgtaa gatgaccatg
2521 gacaagacgg tgcgtcgat gctcgttgc ccagacaaatg tgaccatgg cttgtgttc
2581 tggatggcc gttggggggat gtcggccctc ctctcgatgttgc acactgaccg ctccggc
2641 cacgttggag ggacccttgg ccagtttac caggaggatc tctggggatc tccagcagca
2701 tcagatgtacg gcaatccgcac gctggggatgttccggatgttgc accactctgc caccagagag

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2761 cgccaggctgg attaccagga ggggcccccg ggagtggaga ttccctgctg gtctgtggag
2821 ctgttagttct gatggaagga gctgtgcaca ccctgtacac tggcttccc cctgcaactg
2881 caggccgcgt tctgggcctt ggaccaccaat ggggaggaaag agtcccactc attacaaata
2941 aagaaaagggtg gtgtgagcctt ggg

Protein sequence for Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITIH4):

MKPPRPRVRTCSKVLVLLSLLAIHQTTAEKNIGIDIYSLTVDSRVSSRFAHTVVTSRVVNRANTVQEATFQMELPKKAFIT
NFSMNIDGMTPGIKEKAEAQAYSAAVAKGKNAGLVKATGRNMEQFQVSVSAPNAKITFELVYEELLKRRLGVYE
LLLKVRPQQQLVKHLQMDIHFEPQGISFLETESTFMTNQLVDALTTWQNKTKAHIRFKPTLSQQQKSPEQQETVLDGNL
IIRYDVDRAlSGGSIQIENGYFVHYFAPEGLTMPKNVVFIDKSGSMSGRKIQQTREALIKILDDLSPRDQFNLIIVFSTE
ATQWRPSLVPASAENVNKARSFAAGIQALGGTNINDAMLMNAVQLLDSSNQEERLPEGSVSLIILTDGDPTVGETNPR
SIQNNVREAVSGRYSLFCLGFGFDVSYAFLEKLALDNGGLARRIHEDSDSALQLQDFYQE VANPLLTAVTFEYPSNAV
EEVTQNNFRLLFKGSEMVAGKLQDRGPVLTATVSGKLPQTQNTFQTESSVAEQAEFQSPKYIFHNFMERLWAYL
TIQQLLEQTVSASDADQQALRNQALNLSLAYSFVTPLTSMVVTKPDDQEQSQVAEKPMEGESRNRNVHGSTFFKYY
LQGAKIPKPEASFSPRRGWNRQAGAAGSRMNFRPGVLSSRQLGLPGPPDVPDHAAYHPFRLAILPASAPPATSNP
DPAVSRVMNMKIEETTMTTQTPAPIQAPSAILPLPGQSVERLCVDPRHRQGPVNLLSDPEQGVETGQYEREKAGFS
WIEVTFKNPLVWWHASPEHVVTRNRRSSAYKWKETLFSVMPGLKMTMDKTGLLLLSDPDKVITIGLLFWDGRGEGLR
LLLRDTDRFSSHVGTLGQFYQEVLWGSPAASDDGRRTLVRQGNDHSATRERRLDYQEGPPGVEISCWSVEL

Figure 12. (Page 32 of 33)

NM_000584. Homo sapiens interleukin 8 (IL8), mRNA.[gi:28610153]

1 ctccataagg cacaaacattt cagagacagc agagcacaca agcttctagg acaagagcca
61 ggaagaaaacc acccgaaagga accatctac tggtgttaaa catgacttcc aagctggccg
121 tggctctttt ggcagccctc ctgattctg cagctctgtg tgaagggtca gtttgccaa
181 ggagtgtctaa agaacttaga tgtcagtgca taaagacata ctccaaacct ttccacccc
241 aatttatcaa agaactgaga gtgattgaga gtggaccaca ctgcgccaa acagaaatta
301 ttgttaaagct ttctgtatggaa agagagctct gtctggaccc caaggaaaac tgggtgcaga
361 gggtgtgtggaa gaagttttt aagaggctg agaattcata aaaaaattca ttctctgtgg
421 tatccaaagaa tcagtgaaaga tgccagtgaa acttcaagca aatctacttc aacacttcat
481 gtattgtgt ggtctgtgtt aggggtgcca gatgcaatac aagattctg gttaaatttg
541 aatttcgtta aacaatgaat agttttcat tgtaaccatga aatatccaga acataacttat
601 atgttaaagta ttattttttaa gaatctacaa aaaacaacaa ataattttta aatataagga
661 ttttccataga tattgcacgg gagaatatac aaatagcaaa attgaggccca agggccaaga
721 gaatatccga actttaattt caggaatttgaa atgggttgc tagaatgtga tatttgaagc
781 atcacataaaa aatgtatggaa caataaaattt tgccataaaag tcaaaiittag ctggaaatcc
841 tggattttt tctgttaaat ctggcaaccc tagtctgctt gccaggatcc acaagtcctt
901 gttccactgt gccttggttt ctccctttt tctaagtggaa aaaagtatfa gcccacccat
961 tacccacag tgatgtgtg aggacatgtg gaagcactt aagtttttc atcataacat
1021 aaatattttt caagtgtac ttataacctt atttattttt tatgtttaa ttaagcatc
1081 aaatattgtt gcaagaattt gggaaaatag aagatgaatc attgattgaa tagttataaa
1141 gatgttagat taaattttt ttaatttttga tattaaatgtg tggttttata gataaaatttc
1201 aatcagggtt tttagattaa acaaacaacaa aattgggtac ccagtttttca ttccatttca
1261 gataaaacaac aaataattttt tttagtataag tacatttttg ttatctgaa attttaatttg
1321 aactaacaat ccttagttgtg tactccccagt ctgttgttgc ccagctgtg tggtagtgc
1381 gtgtgtttt acggaaataat gagtttagaaac tatttttttaca gccaaaactc cacagtcata
1441 attagtaattt tctgtgtgtt tgaaactgtt ttattttgtt caaatagattt cttaataat
1501 tattttaaatgtt actgcattttt taaatacaag gctttatattt ttaacttta agatgtttt
1561 atgtgtgttccaaatttttt ttactgttttgc tgattgtatg gaaatataaa agtaaaatatg
1621 aaacatttaa aatataattt ttgtgtcaag taaaaaaaaaaa aaaaaaaaa

Protein sequence for Interleukin 8 precursor

1 mtsklavall aaflisaalc egavlprsa elrcqckty skpfhpkfik elrviesgph
61 canteiivkl sdgrelcldp kenwvqrve kflkraens

Figure 12. (Page 33 of 33)

M11725. Human C-reactive protein gene, complete cds.[gi:181067]

Protein sequence for C-reactive protein

1 meklcflv1 tslhsagfqt dmsrkavfp kesdtysvsl kapltpkla ftvclhfye
61 lsstrgysif syatkrdne ilifwskdig ysftvggsei lfevpevtva pvhictswes
121 asgivefwvd gkprvrkslk kgytvgaeas iilgqeqdsf ggnfegsqsl vgdignvnwm
181 dfvlspdein tiylggpfsp nvlnwralky evqgevftkp qlwp

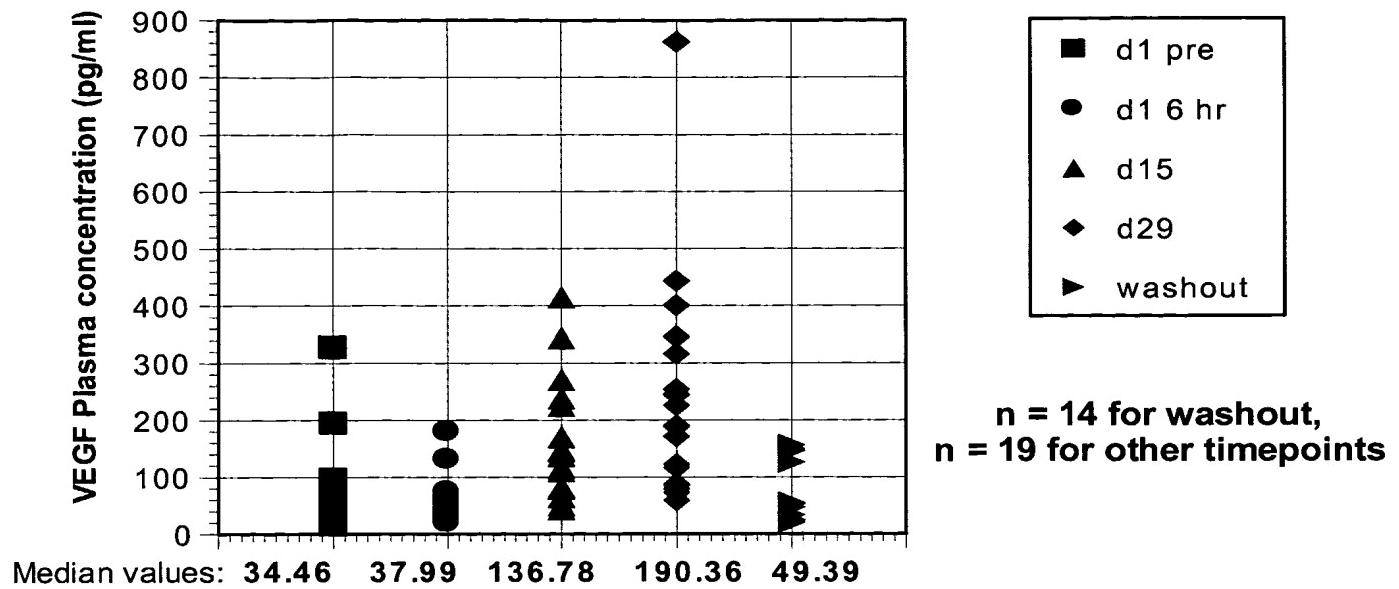
Figure 13.

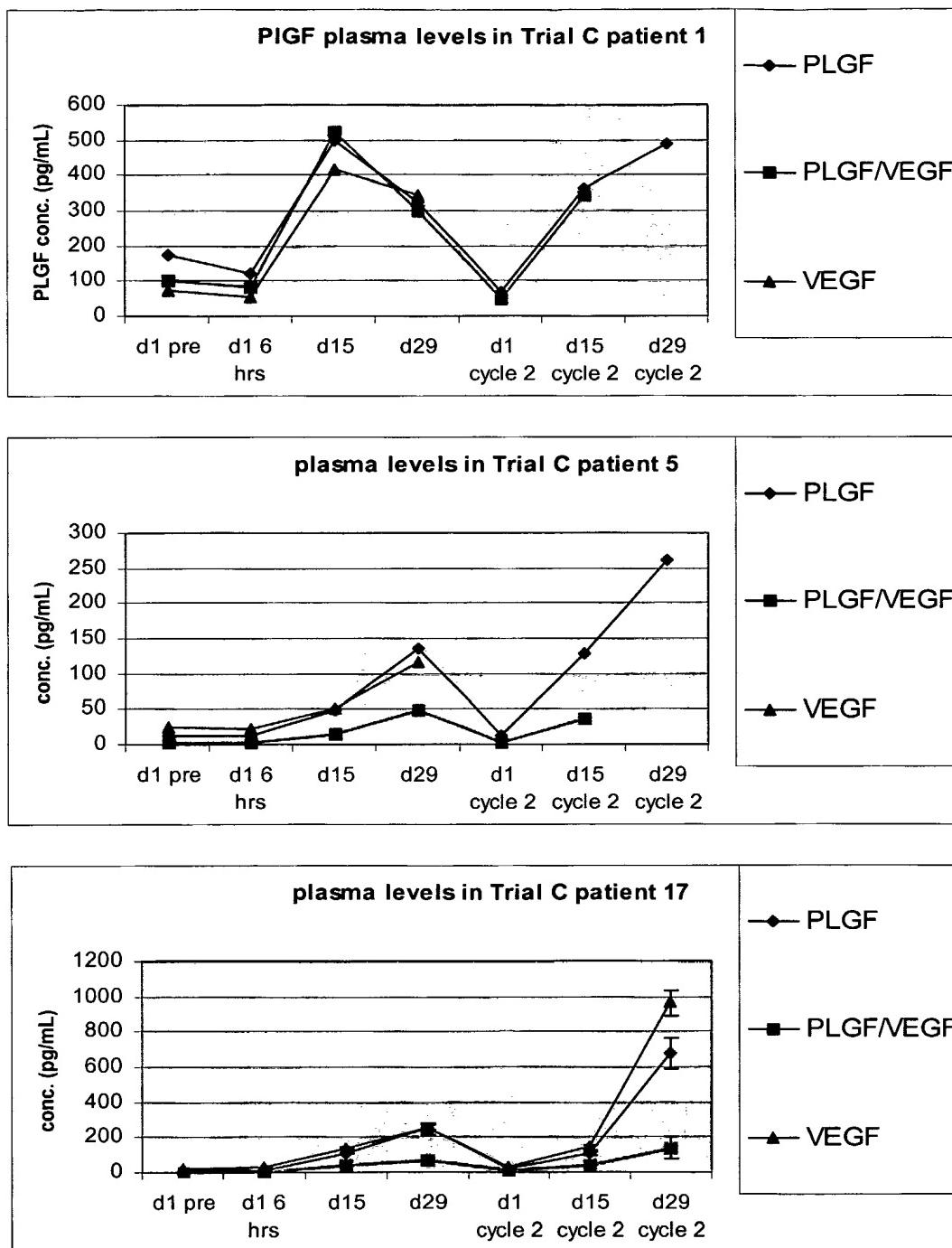
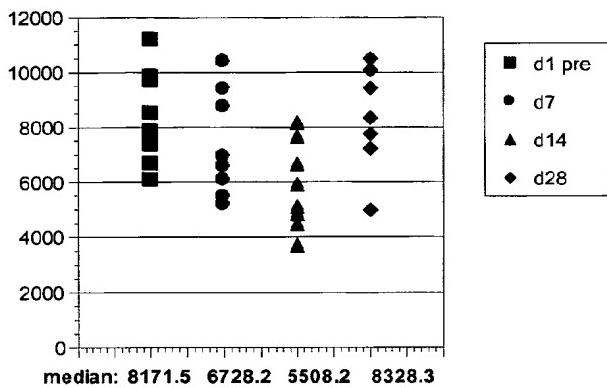
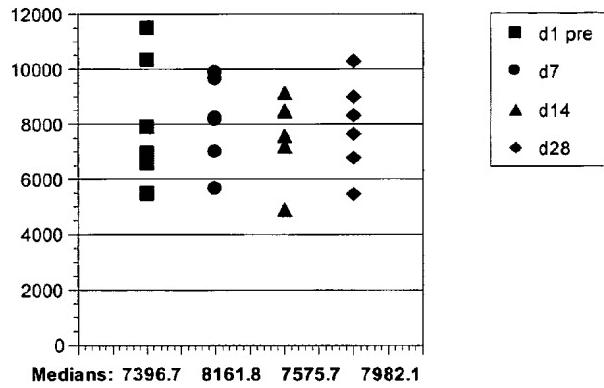
Figure 14.

Figure 15.**sVEGFR2 plasma levels in 50 mg cohort (pts 1-6, 13-14)****sVEGFR2 levels in 25 mg cohort (pts. 7-12)**

Graphs above display plasma levels of sVEGFR2 in individual patients, either 50 mg daily (A) or 25 mg daily (B). The table at right displays results of t-test analysis comparing sVEGFR2 plasma concentrations at end of dosing (d14) to day 1 or at end of cycle 1 washout (d28) to day 1.

d14 v d1 d28 v d1

50 mg cohort	0.0076	0.94
25 mg cohort	0.611	0.87

t-test comparisons of sVEGFR2 levels in two cohorts

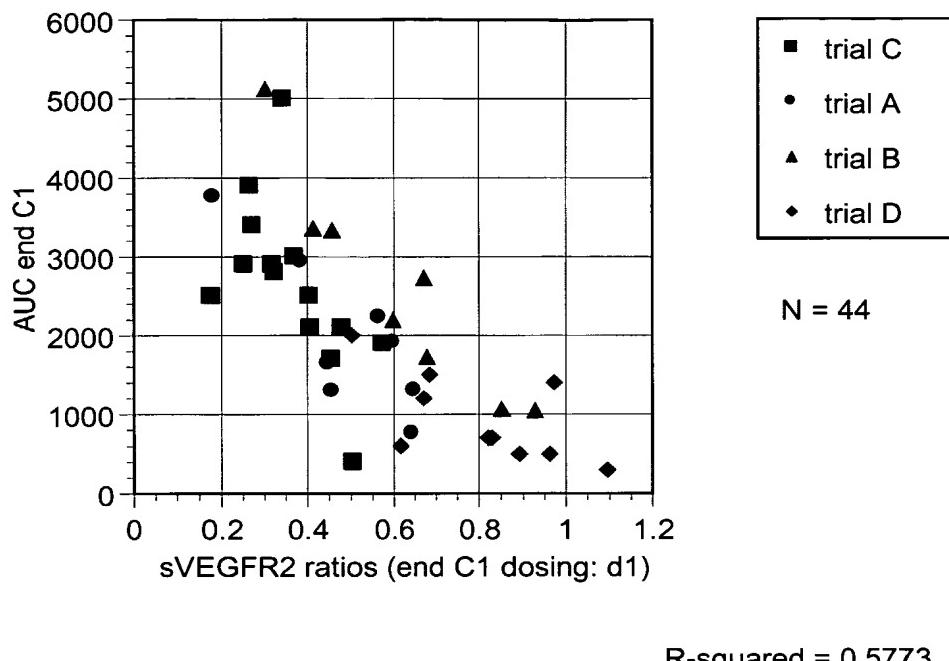
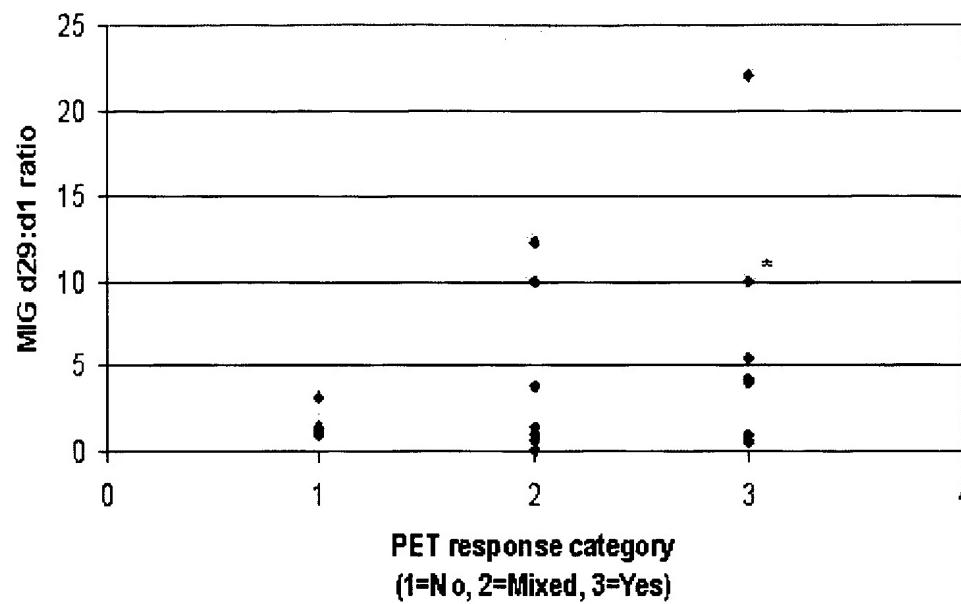
Figure 16.

Figure 17.

1: n = 6, 2: n = 8, 3: n = 8

*estimated minimum ratio

Figure 18.

NP_003367 vascular endothelial growth factor [gi:19923240]

1 mnflswvhw slal ly lhh akwsqaapma egggqnhhev vkfmdvyqrs ychpietlvd
61 ifqeypdeie yifkpsc vpl mrcggcsnde glecvptees nitmqimrik phqgqhigem
121 sflqhnkcec rpkkdrarqe npcgpcser khlfvqdpqt ckcscnths rckarqleln
181 ertcrcdkpr r

Figure 19.

P49763 Placenta growth factor [gi:17380553]

1 mpvmrlfpcf lqlaglalp avppqqwals agngssevev vpfqevwgrs ycralerlv
61 vvseylseve hmfspscvsl lrctgccgde nlhcvpveta nvtmqlkir sgdrpsyvel
121 tfsqhvrcec rhspqrqspd mpgdfradap sflpprrslp mlfrmewgca ltgsqsavwp
181 sspvpeeipr mhpgrngkkq qrkplrekmk percg davpr r

Figure 20.

P35968 Vascular endothelial growth factor receptor 2 [gi:9087218]

1 mqskvllava lwlcvetraa svglpsvsld lprlsiqkdi ltikanttlq itcrgqrld
61 wlwpnnqsgs eqrvevtecs dglfcklti pkvigndtga ykcfyretdl asviyvyvqd
121 yrspfiasvs dqhgvvyyite nknktvvi pc lgsislnvs lcarypekr vpdgnriswd
181 skkgftipsy misyagmvfc eakindestyq simyivvvvg yriydvvlp shgielsvge
241 kvlncart elnvgidfnw eypsskhqhk klvnrdlktq sgsemkkfls tltdgvtrs
301 dqglytcaas sglmtkknst fvrhekpfv afgsgmeslv eatvgervri pakylgyppp
361 eikwykngip lesnhifikag hvltimewse rdtgnytvil tnpiskekqs hvvslvvvvp
421 pqigekslis pvdtsyqygtt qtlctvyai ppphhihwyw qleeeecanep sqavsvtnpy
481 pceewrsved fqgggnkievn knqfaliekg nkvtstlviq aanvsalykc eavnkvgrge
541 rvishfvtrg peitlqpdmq pteqesvslw ctadrstfen ltwyklgpqp lpihvgelpt
601 pvcknltilw klnatmfsns tndilimelk naslqdqgdy vclaqdrktk krhcvvrqlt
661 vlervaptit gnlenqttsi gesievscata sgnpppqimw fkdnnetlved sgivlkdgner
721 nltirrvrke deglytcqac svlgcakvea ffiiegaqek tnleiiilvg taviamffwl
781 llviilrtvk ranggelktg ylsivmdpde lpldehcerl pydaskwefp rdrlklgkp
841 grgafgqvie adafgidkta tcrtvavkml kegathsehr almselkili highhlnvvn
901 llgactkpgg plmvivefck fgnlstyrls krnefvpkyt kgarfrqgkd yvgaipvdik
961 rrldsitssq ssassgfvee kslsdveeee apedlykdfi tlehlicysf qvakgmefla
1021 srkcihrdla arnillsekn vvkicdfgla rdiykdpdyv rkgdarlplk wmapetifdr
1081 vtyiqsdvws fgvllweifs lgaspypgvk ideefcrrlk egtrmraptv ttpemyqtml
1141 dcwhgepsqr ptfselvehl gndlqanaqq dgkdyivlpi setlsmeeds glslptspvs
1201 cmeeeeevcdp kfhydntagi sqylqnskrk srpvsvktfe dipleepevk vipddnqtds
1261 gmvlaseelk tledrtklsp sfggmvpks resvasegsn qtsgyqsgyh sddtdtvys
1321 seeaellkli eivqqtgsta qilqpdsgtt lssppv

Figure 21.

Q07325 Small inducible cytokine B9 precursor (CXCL9) (Gamma interferon induced monokine) (MIG) [gi:585487]

1 mkksgvlfl giillvligv qgtpvvrkgr cscistnqgt ihlqlskdlk qfapspscek
61 ieiiatlkng vqtclnpdsa dvkelikkwe kqvsqkkkqk ngkkhqqkkv lkvrksqrsr
121 qkktt

Figure 22.**NP_001556****interferon-inducible cytokine IP-10 [gi:4504701]**

1 mnqtailicc lifltlsgiq gvplsrtvrc tcisisnqpv nprsleklei ipasqfcprv
61 eiatmkkkg ekrlnipesk aiknllkavs kemskrsp

Figure 23.

O14625 Interferon-inducible T-cell alpha chemoattractant (I-TAC)[gi:7674360]

1 msvkgmaial avilcatvvq gfpmfkrgrc lcigpgvkav kvadiekasi mypsnncdki
61 eviitlkenk gqrclnpksk qarliikkve rknf

Figure 24. (Page 1 of 46)

M33308. Human vinculin mRNA [gi:340236]

Human vinculin mRNA, complete cds

1 gaattccact tctctgtcgc ccggcggtcgc ccgccccgt cgccgcgcg atgcagtg
61 ttcatacgcg cacatcgag agcatctgg agccggggc acaggagatc tccaccctgg
121 tgataatgca cgaggagggc gaggtggacg gcaaagccat tcctgaccc accgcgcgg
181 tggccgcgt gcaggcggcc gtcagcaacc tcgtccgggt tgaaaagag actgtcaaa
241 ccactgagga tcaagatttt aagagagata tgccaccaggc attattaag gttgagaatg
301 cttgcaccaa gcttgtccag gcagctcaga tgcttcagtc agaccctac tcagtgcctg
361 ctgcagatta tctaattgtat gggtaaggg gcatccttc tggaacatca gacctgtcc
421 ttacccctcga tgaggcttag gtccgtaaaa ttatttagagt ttgcaaaaggaa attttggaa
481 atcttacagt ggcagaggtg gtggagacta tggaagattt ggtcacccatc acaaagaatc
541 ttggccagg aatgactaag atggccaaga tgattgacga gagacagcag gagctactc
601 accaggagca cggactgtat tggtaact cgtgaacac cgtgaaagag ttgctgccc
661 ttctcatttc agctatgaag attttgtaa caactaaaaa ctcaaaaaac caaggcatag
721 aggaagctt aaaaaatcgc aattttactg tagaaaaaat gagtgcgtaa attaatgaga
781 taatctgtt gttacaactc acctcttggg atgaagatgc ctggccaggc aaggacactg
841 aagccatgaa gagagcattt gcctccatag actccaaact gaaccaggcc aaagggttggc
901 tccgtaccc tagtgcctcc ccaggggatg ctggtagca ggccatcaga cagatcttag
961 atgaagctgg aaaagtgtt gtaactctgtt caggcaaaa acgcaggggat attctggaa
1021 ctgcaaaat gtagggcag atgactgatc aagtggctga cctcgtgcc agaggacaag
1081 gatcctcacc ggtggccatg cagaaagctc agcaggatc tcagggtctg gatgtgtca
1141 cagaaaaatgaa gtcgcgaacg tggaagccat gaccaactca aacgcagagca
1201 ttgcaaaagaa gatcgatgt gtcagaact ggcttgca tccaaatgggat ggaccggaaag
1261 gagaagagca gattcgaggt gtttggctg aagctcgaa aatagcagaa ttatgtatg
1321 atctctaaaga aagagatgac attctacgtt cccttggggaa aatatctgtct ctgacttcta
1381 aattagcaga tctacgaaga caggggaaag gagattctcc agaggctga gccttggca
1441 aacagggtggc cacggccctt cagaacctgc agacccaaac caaccgggt gtggccaaaca
1501 gcagaccggc caaaggcact gtacaccctt agggcaagat tgaccaagca cagcgggtgg
1561 ttgataatcc cacagtggat gaccgtggag tcggtaggc tgccatccgg gggcttgg
1621 ccgaaggcga tcgtctggctt aatgtatgaa tggggcccta tcggcaagat ctctcgccca
1681 agtgtgaccg agtggaccag ctgacagcccc agctggctga cctggctgcc agagggaaag
1741 gggagagtcg tcaggcacga gcacttgc ctcagctca agactccta aaggatctaa
1801 aagctcgat gcaaggaggcc atgactcagg aagttcaga tggatctcgc gataccacaa
1861 ctcccatcaa gctgtggca gtggcagcca cggcccttc tgatgcctt aacaggaaag
1921 aggtatttga tgagaggcga gctaactttt aaaaccatc aggaaagctt ggtgtacgg
1981 ccgagaaggc ggctcgccgtt ggtactgcta ataaatcaac atggtggaaaggc attcaggcc
2041 cagtgaaagac ggcccggagaa ctcacacccc aggtggctc ggctgctcgt atcttactt
2101 ggaaccttgg aatcaagct gcttatgaaac atttggagac catgaagaac cagtgatcg
2161 ataatgttga aaaaatgaca gggctgggg acgaagccat tgatccaaa tctctgttgg
2221 atgcttcaga agaagcaatt aaaaaagacc tggacaagtg caaggttagct atggccaaaca
2281 tcagctca gatgtctgggtt gctggggcaaa ccagtttgc tcgtccggcc aacccggatcc
2341 tgctggcgc taagagggag gtggagaattt cggaggatcc caagttccgt gaggctgtga
2401 aagctgcctc tgatgtatg agcaaaaacca tctcccaat ggtgtatggat gcaaaagctg
2461 tggctggaaa cattccggac cttggactgc aaaagagctt cttggactca ggtatcgga
2521 tcctggggcgc tggccaaag gtcagagaaag cttccaaacc tcaggagccct gacttcccg
2581 cgcctccacc agacccatgaa caactccgac taacagatga gtttgcctt cccaaaccac
2641 ctctgcctga aggtggggcgc cttccacca ggcctccacc accagaggaa aaggatgttgaag

Figure 24. (Page 2 of 46)

2701 agttccctga gcagaaggcc ggggaggtga ttaaccagcc aatgatgatg gctgccagac
2761 agctccatga tgaagctgc aatggtcca gcaaggccaa tgacatcatt gcagcagccaa
2821 agcgcattgc tcgtcgatg gctgagatgt ctggctgg aagagggggc agtgtacca
2881 agcgggact cattcagtgt gccaaggaca tcgccaaggc ctcagatgag gtgactcggt
2941 tggccaagga gggtgccaag cagtgcacag ataaacggat tagaaccaac ctcttacagg
3001 tatgtgagcg aatccccacc ataagcaccc agctaaaaat cctgtccaca gtgaaggccaa
3061 ccatgtggg ccggaccaac atcagtgtat aggagtctga gcaggccaca gagatgctgg
3121 ttcacaatgc ccagaacctc atgcagtctg tgaaggagac tgtgcgggaa gctgaagctg
3181 cttaatcaa aattcgaaca gatgctggat ttacactgcg ctgggttaga aagactccct
3241 ggttccatgtt ggcacccccc tgagccctggc tggcacagaa acctctacta aaaagaagga
3301 aaatgatctg agtccccaggaa gctgcccaga gtgtgggaa gctgaaaaat cacatccctgg
3361 cctggccat cagaaaggaa tggggccctc ttcaaattag aagacattt tactctttt
3421 tcatggacac ttgaaatgt gttctgtat aaaggctgtt ttcataaca cagttacact
3481 tggccacccctt ctatccaaat aggccagactg gtttcttag ccatggactt cacataagct
3541 cagaatccaa gtgaacacta gccagacact ctgcctgtcc ctgtccctt aggggacact
3601 tccctctgtt tctttccctt tggccatccat tcactttcc agaatccaa gacccaggc
3661 ccaggccaaat cagttactaa gaagaaaatt gtgtgcctc cccaaatgtt ttgagctt
3721 ccatgttgcg gccaaccata cttcccttcc ctgggctgtg ctacctgggt cctttcaga
3781 agtgagctt gctgtacag gggaaagggtgg cctctgtgaa gccccagcat atggggccct
3841 ggattcattt cctggccctt ctcagttaa tccctcttagt ttcccacaat ataaaactgt
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3961 caatgtctgt gctagggaaa ctccccgtcc catatctgc ctcagccgc caaggtagcc
4021 atccccatgaa cacactgtgt cctgggtctc tctgcccactg gaagggcaga gtggccagg
4081 tggccctg ccatctccc agcaggccaa cttccggcac tccatgttta gtcactgcct
4141 gcagagggtct gtgtgaggc cttatcatc attcttagct cttaaattttt cattttgagc
4201 tggaaatgtt cattttaaat ttaacaaaaa catgtctctt atatctgtt tttttagcc
4261 tccctccaca tcccttctaa acaagattt aaagacatgtt aggtgtttgt tcatctgtaa
4321 ctctaaaaga tcccttttta attcagtcctt aagaaagagg agtgctgtc cccaaatgt
4381 gtttaatggc aaggcagccc tggctgttgc acacttcctt cctaaggagg agtggattt
4441 gcagactaga attctgtgc tggctgttgc agaatcatgg gaaatactac tccctgtt
4501 cttccctcc tggccatccaa tacaaccaag ctctctgtt cttttttttt gatgggg
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4621 agaggccagt gttccctttt tggctgttgc ttttttttccatggc cccatgg
4681 cttttttttt cccaaagccatgg aaccagatgaa gtaaaggatg aagaacccctt cctggccatc
4741 cttccctcc accccatcgctt gttttttttt tcccaacatc gaatgtgtac aacttaatgt
4801 ggtcccttac actcaggctt tcaacttttcc ctttttttccatggc cccatgg
4861 cttccatggc tttttttttt tggctgttgc ttttttttccatggc cccatgg
4921 atgaatctat gccaaagatc acttgggtt ttttttttttccatggc cccatgg
4981 agaaaaatca tggctgttgc ttttttttttccatggc cccatgg
5041 atggccggatg tggcccttcc caatatcagt gtttttttttccatggc cccatgg
5101 aa

Figure 24. (Page 3 of 46)**Protein Sequence of Human vinculin:**

MPVFHRTIESILEPVAQQISHLViMHEEGEVGDKAIPDLTAPV
AAVQAAVSNLVRVGKETVQTTEQILKRDMPPAFIKVENACTKLVQAAQMLQSDPYSV
PARDYLIDGSRGILSGTS DLLTFDEAEVRKIIRVCKGILEYLTVAEVVETMEDLVTY
TKNLGPGMTKMAKMIDERQQELTHQEHRVMLVNSMNTVKELLPLISAMKIFVTTKNS
KNQGIEEALKNRNFTVEKMSAEINEIRVLQLTSWDEDAWASKDTEAMKRALASIDSK
LNQAKGWLRDPSASPGDAGEQAIRQILDEAGKVGELCAGKERREILGTCKMLGQMTDQ
VADLRARGQGSSPVAMQKAQQVSQGLDVLTAKEVNAARKLEAMTNQSIAKKIDAAQ
NWLAADPNGGPEGEEQIRGALAEARKIAELCDDPKERDDILRSLGEISALTSLADLRR
QGKGDSPEARALAKQVATALQNLQTKTNRNAVANSRPAKAAVHLEGKIEQAQRWIDNPT
VDDRGVGQAAIRGLVAEGHRLANVMMGPYRQDLLAKCDRVDQLTAQLADLAARGEGES
PQARALASQLQDSLKDLKARMQEAMTQEVSDFSDTTPIKLLAVAATAPPDAPNREE
VFDERAANFENHSGKLGATAEKAAA VGTANKSTVEGIQASVKTARELTPQVVSARIL
LRNPGNQAA YEHFETMKNQWIDNVEKMTGLVDEAIDTKSLLDASEEAIKKDLDKCKVA
MANIQPQMLVAGATSIARRANRILLVAKREVENSEDPKFREAVKAASDELSKTISPMV
MDAKAVAGNISDPGLQKSFLDSGYRILGAVAKVREAFQPQEPDFPPPPPDLERQLRLTD
ELAPPKPPLPEGEVPPPRPPPPEEKDEFPEQKAGEVINQPMMMAARQLHDEARKWSS
KGNDIIAAAKRMALLMAEMSRLVRGGSGTKRALIQCAKDIAKASDEVTRLAKEVAKQC
TDKRIRTNLLQVCRIPTISTQLKILSTVKATMLGRTNISDEESEQATEMLVHNAQNL
MQSVKETVREAEAASIKIRT DAGFTLRWVRKTPWYQ

Figure 24. (Page 4 of 46)

M90354 Basic Transcription Factor 3 Homologue

1 aagcttttag ttcccttaa tcataaaaagc cactgctaa ctaaaactag agatagctca
61 agctatcta ttttaaaggc ttgtctcaa tggtccctt ccctgaatc ccagtagagt
121 agccaattgt ctgaaacccg ctggattta gcaatgaaac acctcagtc tggccaaacc
181 aagacagtgg gtctcaggaa acatcttca tcctaataaa ggcaaaattaa ctacagtta
241 ccctgaaca acatgggggt tatgggtct gacttccat gcagtaaaaa atctgggtat
301 aacctcgat tccacaaaaa ctttgctaat agcctaact gttactgga agccttacca
361 ataacacata cagttgatta acacatata tttatgttatt atattacaat aaattaagct
421 agagaaaaga aatgtattc ctttgctgc catctgcctt ccctgtgtc ttctaatctc
481 agctggctc acccggact ccccaagtgc caaccctagt cccccacgca gcccccttttc
541 cactcagata agatgaaaga aacaatcatg aaccaaaaaac tcaccaaacg gcaagcagaaa
601 gtgcacactg gtggaaagg aactgctcac aggaaaaagg tggttcacag catctgagac
661 gctgtgtttt agggcaagta ggcccccttg acacccttgg tggtgaactc atgagggttt
721 gaatgtccag ggacattggc caatatcaa agaacttta aagtctgtt ggttaaggatc
781 ttcttgactt cagggacaaa acagcaatgg aaccaatcca gaaaaagggt tctattgtc
841 caggccctct ggtacaacca aaagactggc agctggcatt tatctgttcc ctcaaggct
901 cagaggtaa cggttttata cataagggtt gtcctgtatca taaaccttgc gacagcagag
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1321 tgaatgttact tttttatgttact tttttatgttact tttttatgttact tttttatgttact
1381 tatgttatgttact tttttatgttact tttttatgttact tttttatgttact tttttatgttact
1441 ctaatatttt

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J04111 Human c-jun proto oncogene

1 cccggggagg ggaccgggga acagaggggc gagaggcgtg cggcaggggg gagggttagga
61 gaaagaaggg cccgactgtg ggagggcagc ggagcattac ctatcccgt gacgcctccgc
121 gggcccgag aagaatcttc tagggtgtag tctccatggt gacggccggg cccgcccccc
181 tgagagcgac gcgagccaat gggaaaggcct tggggtgaca tcatgggcta ttttagggg
241 ttgacttgta gcagataagt gttagctcg ggctggataa gggctcagag ttgcacttgag
301 tgtggctgaa gcagcgaggc gggagtggag gtgcggag tcagggcagac agacagacac
361 agccagccag ccaggtcgcc agtatagtc gaactgcaaa tcttattttc tttcacctt
421 ctctctaact gccccagagct agcgcctgtg gctccgggc tgggttgc ggagtgtcca
481 gagagccctg tctccagccg gccccggag gagagccctg ctgcccaggc gctgttgaca
541 gcggcgaaa gcagcggtac cccacgcgcc cgccggggga cgtcgccgag cggctgcagc
601 ageaaagaac ttcccgccg gggaggaccg gagacaagtg gcagagtccc ggagcgaact
661 ttgcaagcc ttccctgcgt cttaggcctc tccacggcgg taaagaccag aaggccggcgg
721 agagccacgc aagagaagaa ggacgtgcgc tcagctcgc tcgcacccgt tggtaactt
781 gggcgagcgc gagccgcgc tgccggcgc cccctcccc tagcagcggaa ggaggggaca
841 agtgcgtgga gtccggcgg ccaagaccg cgcggccgc gcaactgcag ggtccgcact
901 gatccgctcc gcggggagag cgcgtctt gggaaagttag ttcgcctcgc gactccgagg
961 aaccgtcgc cccgaagagc gtcagttag tgaccgcac ttctcaaagc cgggtacgc
1021 ggcgagtcg acaagtaaga gtgcgggagg catcttaatt aaccctgcgc tccctggagc
1081 gagctggta ggagggcgcgca gcggggacga cagccagcgg gtgcgtgcgc tcttagagaa
1141 acttccctg tcaaaggcgc cggggggcgc gggtgtcccc cgttgccag agccctgttg
1201 cggccccgaa acttgtgcgc gcacgcacaa ctaacctcac gtgaagtgc ggactgtct
1261 atgactgcaa agatggaaac gacccttat gacgatgccc tcaacgcctc gttccctccg
1321 tccagagcgc gacccttatgg ctacagtaac cccaaagatcc tgaacacagag catgaccctg
1381 aaccctggccg acccagtggg gagectgaag cgcacccctc ggcaccaagaa ctggaccc
1441 ctacacgcgc cgcacgtggg gtcgtcaag ctggcgtgc cgcagctggaa ggcctgata
1501 atccagtcga gcaacgggca catcaccacc acgcggaccc ecacccagtt cctgtgcccc
1561 aagaacgtga cagatgaga ggaggggttc ggcggggct tcgtgcgcgc cctggccgaa
1621 ctgcacagcc agaacacgc gcccagcgc acgtcgccgg cgcagccgg caacggggca
1681 ggcattggg ctccgggtt agcctgggtg gcagggggca ggcgcagcgg cggcttcagg
1741 gccagcctgc acagcgagcc gccggctac gcaaaacctca gcaacttcaa cccaggcgcg
1801 ctgagcagcgc gcggcggggc gccccttac ggcgcggccg gcctggcctt tcccgccaa
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1981 cccctgtccc ccatcgacat ggagcctcag gagggatca aggccggagag gaagcgcatg
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2161 ctcaaggaaac aggtggcaca gcttaaacag aaagtcatga accacgttaa cagtgggtgc
2221 caactcatgc taacgcagca gtgcacaaaca tttgaagag agaccgtcgg gggctgaggg
2281 gcaacgaaga aaaaaaaaaa cacagagaga cagacttgag aacttgacaa gtgcgcacgg
2341 agagaaaaaa gaagtgtccg agaactaaag ccaagggtat ccaagttgga ctgggttcgg
2401 tctgacggcg ccccccagtgt gcacgagtttgg gaaggacttg gtgcgcctt cccttggcgt
2461 ggagccaggg agcggccgc tgcggctgc cccgccttgc gcacggggctg tcccccgcgc
2521 aacggaaacgt tggactttcg ttaacatttg ccaagaactg catggaccta acatcgatc
2581 tcaatcgat taaaaggggg gagggggagg gggttacaaa ctgcaataga gactgttagat
2641 tgcttctgtt gactcccta agaacaacaa gcgggggag ggttggggag gggccggcagg
2701 agggagggtt gtgagagcga ggctgaccc acagatgaac tcttctggc ctgcttctgt
2761 taactgtgtt gtttacatata tttttttt aatttgcattttt aagctgatca ctgtcaatata

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2821 acagcttcat gcctttgtaa gttatttc ttgttgttgc tgcccaatgt
2881 tgtttgtaaa taagagattt ggagcactct gagtttacca ttgtataaa agtatataat
2941 tttttatgt ttgttctg aaaattccag aaaggatatt taagaaaata caataaaacta
3001 ttggaaagta ctcccctaac ctctttctg catcatctgt agatcctagt ctatcttagt
3061 ggagttgaaa gagttaaagaa tgctcgataa aatcactctc agtgcttc ttactattaagc
3121 agtaaaaact gtctctatt agacitagaataaaatgtac ctgtatgtacc tgatgtatag
3181 tcaggcctca tactccacgc tccccagcg tacttatatg gaattgttta ccaaaggcta
3241 gtgcgtatgtt tcaggaggct ggaggaaggg ggggtgcagt ggagaggac agccactga
3301 gaagtcaaac atttcaaaatgttggattgca tcaagtggca tttgtgtga ccatttataa
3361 tgtagaaat ttacaatag gtgttttttc tcaaaggcagg aattgggtgc agattttaca
3421 aaagatgtat cttccaattt tggaattttc ttgttgcacaa ttccctagata aaaagatggc
3481 ctgttgcataa tgaatattta taacagcatt ctgtcacaat aaatgttattt aaataccat
3541 aacagatctt gaattgttc cctttactac ttgttgcacaa ttccctagata tactgaagtt
3601 ttatattttta gttgttgagg tt

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K00650 Human c-fos proto-oncogene

1 gcaggaacag tgcttagtatt gtcgagccc gagggctgga ggtaggggaa tgaaggctg
 61 ctccacgc ttgcactgaa ttgggctag aatggggat gggggtaggg ggcattct
 121 tcgggagccg aggcttaagt cctcggttgc ctgtactcga tgccgttct cctatctctg
 181 agcctcagaa ctgtcttag tttccgtaca aggtaaaaa ggcgtctct gccccatccc
 241 ccccgaccctc gggacaagg gtccgcattt aaccagggtgc gaatgttctc ttcattctg
 301 cggcgttccc gcctccctc ccccaagccgc gggcccccgc tccccccgca ctgcaccctc
 361 ggtgtggct gcagcccgcg agcagttccc gtcaatccct cccccccttac acaggatgtc
 421 catatttagga catctcgctc agcaggttt cacggcctt ccctgttagcc ctggggggag
 481 ccattcccgaa aaccctcat ctggggggc ccaagagacc ttgagacag gaactgcgaa
 541 atgctcacga gattaggaca cgcgccaagg cggggcagg gagctgctg cgttgggac
 601 gcagccgggc ggccgcagaa ggcgcaggc cgcgcgcaca ccccttggc gccaccgtgg
 661 ttgagccctg gacgttatac ctcattata aaacgttctg tataaaagca gtggctgctgg
 721 cgccctgtac tccaaaccga tctgcagcga gcaactgaga agccaagact gagccggcgg
 781 cccggcgca gcgaacgacg agtgcggctg ctccatccca gctctgttc acagcgccca
 841 cctgtctccg cccctcgcc ctcgcggcgg ctggcttaa ccggccacgtat gatgttctg
 901 ggctcaacg cagactacga ggcgtcatcc tcccgctgca gcagcgcgtc cccggccggg
 961 gatacgctctt acttacca ctcaccgcga gactcccttccagcatggg ctgcctgtc
 1021 aacgcgcagg taaggtggc ttcccgctgc cgcggggccg gggcttggg gtgcggagg
 1081 aggagacacc gggcgggacg ctccagtaga tgagttaggg gctcccttg gcttgaggg
 1141 aggctgcgtt ggccggagcg gtgcggctc gggggcttgg gacttgcgtc gagcgcacgc
 1201 acgttgcctactaaat tggttcccccc ttggggagggc aggttgcgtc tgagcaacct
 1261 ctggctgca ctccaggacg gatctctgac attagctgga gcagacgtgt cccaaagcaca
 1321 aactcgctaa ctagagctg gcttccctgg gggagggttggca gaaagcggca atccccctc
 1381 ccccgccagc ctggagcacg gaggaggat gaggaggaggg ggtgcagcgg ggggtgtgt
 1441 aaggcagttt cattgataaaa aagcgagttt attctggaga ctccggagcg ggcctgtgt
 1501 cagcgcagac gtcaggataa ttataacaa acccccttc aagcaagtga tgctgaaggg
 1561 ataacggaa cgcagcggca ggatggaaga gacaggact ggcgtcggaa atgcctggaa
 1621 gggaaagggg gagaccccttc atccaggatg agggacattt aagatgaaat gtccgtggca
 1681 ggatcggttc tcttcactgc tgcatgcggc actgggaact cgcggccactt gtgtccggaa
 1741 cctgtctgtt ctcgtcgctt tcccttctt gtttttttctt aggactctg caeggacatcg
 1801 gccgtctcca gtgcctactt cattcccaac gtcactgcctt tctgcggccatcg
 1861 cagttggctgg tgcagccgc ctcgtctcc tctgtggccc catcgccagac cagggccct
 1921 cacccttccg ggttcccgcc cccctccgtt gggcttactt ccagggttgg cgttgtaaag
 1981 accatgacag gaggccgagc gcagacgtt ggcaggaggg gcaagggttgg acagggttgg
 2041 aactcttagcg tactcttctt gggaaatgtgg gggctgggttgg ggaaggcggcc cggagatgc
 2101 aggagcccttccg tacagaggat gaagccactg atggggctgg ctgcacatcc gtaactggaa
 2161 gcccggccttccg caagccattt ccattccaaac tcaagactctg agtctccatcc taagaagtt
 2221 tctcatagtt tttccctaa gtttttttccatcc gcatgttttcc agactgggtt ctttttttt
 2281 ctcttgctga ggttccctttaaaatgcaaa gtcacaccta ttctgtcaact gcaggtcaga
 2341 aatggtttca cagttgggttccaggaagca gggaaatgttcc agggccactt tctactgggg
 2401 tgggtgaatg gaggttgcgttcc cagacacttt tactgtatgtt cgggtttttt tttttttt
 2461 tctgttttccatcc tccagaagaa gaagagaaaa ggagaatccg aaggaaagg aataagatgg
 2521 ctgcagccaa atgcgcacac cggaggagg agctgactgta tacactccaa ggcgttaggtt
 2581 ctctgtgggt tgcctttttttaaaatgcaaa gggaaatgttcc aggttgcgttcc ataggcc
 2641 ttggatgaaatgcaaa ctgtgttccatcc ttttttttttccatcc tatacaggag acagaccaac
 2701 tagaagatgaaatgcaaa gaaatgttcc aggttgcgttcc atggggccaa cttgtgttcc
 2761 aacttagatgttccatcc ttttttttttccatcc gtcacccatcc gatccctgttccatcc

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2821 tcccagaaga gatgtctgt gcttcccttg atctgactgg gggcctgcca gaggttgc
2881 ccccgagtc tgaggaggcc ttacccctgc ctctcctaa tgacccttag ccaagccct
2941 cagtggAACCT tgtcaagAGC atcAGCAGCA tggAGCTGAA gACCAGGCC ttGATGACT
3001 tcctgtcccc agcatcatcc aggCCAGTG ctctgAGAC AGCCCGCTCC gtCCAGACA
3061 tggacctatc tgggtcccttc tatgcAGCAG actGGGAGCC tctgcACAGT ggCCCTCTGG
3121 ggtggggcc catggcaca gagctggAGC ccctgtgcAC tccgggtggc acctgtactc
3181 ccagctgcac tgcttacacg tcttccctcg tcttcaccta ccccAGGGT gactccTCC
3241 ccagctgtgc agctgcccac cgcaAGGGCA gcAGCAGCAA tgAGCCTTC tctgactcGC
3301 tcagctcacc cacgctgtgc gcccTGTGAG ggggCAGGGA aggggAGGCA gcccgcACCC
3361 acaagtgcCA ctgcccAGC tggTGCATTA cAGAGAGGA aaACACATCT ccCTAGAGG
3421 gtccctgtAG acctAGGGAG gacTTATCT gtGCGTgAAA cacACCAGGC tggggccTc
3481 aaggACTGA aAGCATCCAT gtGTTGGACTC aAGTCCttAC ctCTCCGGA gATGTA
3541 aacGcatggA gtGTTGATTG ttCCAGTGA cACTCAGAG AGCTGTTAGT tagTAGCATG
3601 ttgagccagg ctgggtctg tgcTCTTT ctCTTCTCC ttGTTCTCT catAGCATT
3661 actaatctat tgggtcattt attGGAATTt acctGGTGT GGATATTTC aaATTGATC
3721 tagTGCAGCT gatTTAACAt aAAACTACTG tGTTCTGGC aATGTTGTT tCTGATTAGA
3781 aatGACCAAT attATACTAA gaaaAGATAc gACTTATTt tCTGTTAGt agaaATAAAT
3841 agCTATATCC aITGACTGTa gTTTCTTC aACATCAATG tTCATGTA tGTTACTGT
3901 catGcattgt tgaggTGGtC tgaatGTTCT gacattaACa gtttCCATG aaaACGTTT
3961 attGTTTT taATTATTt attAGATGG attCTCAGAT attTATATTt ttTTTTT
4021 ttTTCTACC ttgaggTCTT tgacatGTg gaaAGTGAAT ttGAATGAAA aATTtAAGCA
4081 ttGTTGCTT attGTCCTAA gacattGTCA atAAAGCAT ttaAGTGAAT tgCgACCAAC
4141 ctTGTGCTCT tTCATTCTG gaAGTCTGT aAGTTCTGA aAGGTATTt tGGAGACCAg
4201 ttGTCAGA aGGGTAGCTG ctggaggGGG acACACCCtC tGTCtGATCC ctTCAAG
4261 aggacaAGGA aactataGAG ctGATTtAG aATTTtAC aAATACATGC ctTCCATTG
4321 aATGCTAAGA ttTCTACTG ctTCTGGGGA cgggAAACCG ctGtGTAACA gCTTTGTTG
4381 gaatacATTt ttTCTGTTt agTACTCGCA gggggAAATA ttAAATTt tGTTGtCTAA
4441 tattaaATTc agatGTTTG atCTTAAAGG aACCCtTAA gCaaACAGAA CCTAGTTG
4501 tacagactat ttAACTTT tattCTACa AAATCACGTG gaggGTtAtt ctAcTTCAA
4561 gatgagAAAGA ttGAAGAATG ttGAGAATAA aCAACTTTt tGATATTCCG ttATCGGCA
4621 tagAAATCTC ctGCTCGTA tGtATCCAG cAGGCTGAAC tGCCTTGTa tacTTGTT
4681 aaaaaAAATTt tcaggCCGGG cgcggTGGC catGCTGTA atCCtAGCAC ttGGGAGGC
4741 cgaggcAGGC ggatCACCTG aggtCggggAG ttCgAGACCA gCCTGACCA catggAGAA
4801 ccccgCTTT actaaaaATA caAAATTAGC ctggTGTGTT ggtGcatGCC tGTAATCCTA
4861 gCTACTTGAG aggCTGAGAC aggAAAATCA ctTGAACtCG ggaggCggat gttGcAGCg
4921 actgagATTG CGCCATTGCA ctCCAGCTG ggCAACAAAGA ttGAAACTCT ttTTAAAAAA
4981 AAAAGTTtC actAAATGT acATTtttTt GtACTCTTTt ATTCTCGAAA gggAAGGAGG
5041 gCTATTGCC tATCCCTTt TAATAAATGC ATTGTTGTTt CTGTTCTC TAATACCATA
5101 tGCCCTCAT tcAGTTATA tGgggCggAA tGggggAGA AAAAGTTGCT cAGAAATCAA
5161 aAGATATCTC AAACAGCACA AATAATGGCT gatGTTCTG CAAACAAAAA gttACATAAT
5221 agCTAAGAA ggAGAAGTCA acATGACTCT GAACAAGCTT TAACTTAGAA ACTTTATCAT
5281 cttaAGGAAG AACGTGACCT ttGTCAGGA cgtCTGTGTT aATGGGGCAC ttACACACAC
5341 atGCACACGT ACAAAACACAA gggAAAGGAG ACCGCCCTTC tGCCtCTGCT CGCAGTATC
5401 acgcaggcac catgcactat gtttacac acactGGGTG gaAGAAGAGC ttCAGCGCCA
5461 gCTTCTAAT gCTTGGTGA TAATGAAAAT cACTGGGTGc ttATGGGGTG tCATATTCAA
5521 tGAGTTAAA AGTTtAATT AAAAATGACA gTTTACTGA ggttGATGTT CTGCTATG
5581 atATCTCTGC CCCTCCCTAA AAAATGGACA ttAAAAGCA ACTTACCGCT CTTAGATCA
5641 ctCTATATC ACACACCACt tGGGGTGTGTT ctGCTGCTAG ACTTGTGATG ACAGTGGCCT
5701 taggatCCCT ttGTCGTtG CAAAGGGCAAA atATTTATAA GCTTTAAAT ATACCTAAAC

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5761 taaaatacaga attaatataa ctaacaaaca cctggctctga aataacaagg tgatctacc
5821 tggaaggaac ccagctggtg ggccaggagc ggtggctcac acctgtaatt ccagcac
5881 gggaggctga gacaggagga tcactggagt ccaggagttt gagaccagcc tggcaacat
5941 ggcaaaaacc agtgtgcttc tggtgtccca gctacactac tcaggaggct gaggcaggag
6001 tatgacttga gcctgggagg gggagggtgc agagaactga tattgcacca ccactgcact
6061 ccagcctggg tgacacagca aaaccctatc taaaaaaaaaaaaaaa aaggaaccca
6121 gctggccct gtaggtgtgc aataataaca accagaggaa gaaaaggaag acgattccc
6181 agatgaagaa gggcagctgg accttcggac

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NM_080422 Homo Sapiens Protein Tyrosine Phosphatase, non-receptor type 2

1 gtcggggcgc cgagtctgct cgtacgtcc cgacgttcca ggtactttcc ccacggccga
61 cagggttgg ctgtggggcg gggcgccgc cgcagcgcgc atgcgccga gcgcgcgc
121 tctccccga tcgtcgcccc cctgagccctc tccgcggcg caggctctgc tcgcgccagc
181 tegctcccgc agecatgccc accaccatcg aecgggagtt cgaagagttt gatactcage
241 gtcgctggca gccgctgtac ttggaaattc gaaatgagtc ccatgactat cctcatagag
301 tggccaagtt tcacaaaaac agaaatcgaa acagatcacag agatgtaaac ccatcatgatc
361 acagtcgtt taaactcgaa aatgtcgaga atgattatataatgcccattt ttagttgaca
421 tagaagaggc acaaaggagt tacatcttaa cacagggtcc acttcctaaac acatgtgcc
481 atttcggct tatggtttg cagcagaaga ccaaagcagt tgctatgtc aaccgcattt
541 tggagaaaga atcggtaaaat tggtcacagt actggccaaac agatgaccaa gagatgttgt
601 ttaaagaaac aggattcagt gtgaagtc tgctagaaga tgtaagtcg tattatacag
661 tacatctact acaatttagaa aatatcaata gtggtaaac cagaacaata ttcacttcc
721 attatactac ctggccagat ttggagtc ctgaatcacc agtttcattt ctcaatttct
781 tgtaaagt gagagaatct ggcccttga accctgacca tggccctgctg tgatccact
841 gtagtgcagg cattggggcgc tctggcacct tctcttggt agacacttgt ctgttttg
901 tggaaaaagg agatgtat aacataaaac aagtgtact gaacatgaga aaataccgaa
961 tgggttatt tcagacccca gatcaactga gatttcata catggctata atagaaggag
1021 caaaaatgtat aaagggagat tctagtatac agaaacgtt gaaagaactt tctaaggaaag
1081 acttatctcc tgcctttgtat cattcaccaaa acaaaaataat gactgaaaaa tacaatggga
1141 acagaatagg tctagaagaa gaaaaactga caggtgacccg atgtacagga ctttccttca
1201 aaatgcaaga tacaatggag gagaacagtg agagtctct acggaaacgtt attcgagagg
1261 acagaaaggc caccacagct cagaagggtc agcagatgaa acagaggctt aatgagaatg
1321 aacggaaaaag aaaaaggcca agattgtacag acacctaata ttcatgactt gagaatattc
1381 tgcagctata aattttgaac cattgtatgtg caaagcaaga cctgaagccc actccggaaa
1441 ctaaagttagt gtcgctaaac cctcttagatt gcctcacagt tgttgttta caaagtaaac
1501 ttacatcca ggggatgaag agcaccacc accgagaagac ttgcagaac ctttaattgg
1561 atgtgttaag tggtttat gactgtatga aatgtagaaa gatgtacaag aaataaaatta
1621 ggagagatta ctttgtatgt tactgcccattt cctactgtat tttatactt tttggcagca
1681 ttaaatattt ttgttaataa aaaaaaaaaaaa aaaa

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M68520 Human cdc2-related protein kinase

1 ggaggcggca acattgttc aagttggcca aattgacaag agcgagaggt atactgcgtt
61 ccatccgac cggggccacg gtactggcc ctgttcccc ctctcgccccc cccgagagcc
121 agggtccgccc ttctgcagggt tcccaagggc cccgctccag ggcgggctg acccgactcg
181 ctggcgcttc atggagaact tccaaaaggt ggaaaagatc ggagagggca cgtagggagt
241 tgtgtacaaa gccagaaaca agttgacggg agaggtgggt ggcctaaga aaatccgcct
301 ggacactgag actgagggtg tgcccaatcgagatctc tgcttaaggaa
361 gcttaaccat ctaataatttgc tcaagctgtt ggtatgcatt cacacagaaaa ataaactcta
421 cctgggtttt gaatttctgc accaagatctt caagaaatttgc atggatgcct ctgtctcac
481 tggcattctt ctccccctca tcaagagcta tctgttccag ctgtccagg gcctagctt
541 ctgcattctt catcggttcc tccaccgaga ccttaaacctt cagaatctgc ttataacac
601 agagggggcc atcaagctag cagacttgg actagccaga gctttggag tccctgtcg
661 tacttacacc catgaggtgg tgaccctgtt gtaccgaget cctgaaatcc tcctgggtcg
721 caaatattat tccacagctg tggacatctg gagectggc tgcatcttg ctgagatgg
781 gactgcccgg gcccatttcc ctggagattc tgagatttgc cagctctcc ggtatttcg
841 gactctgggg accccagatg aggtgggtg gccaggagttt actctatgc ctgattacaa
901 gccaagttc cccaagtggg cccggcaaga tttagttaaa gttgtacctc ccctggatga
961 agatggacgg agctgttat cgcattatgtt gcactacgac cctaacaagc ggattcggc
1021 caaggcagcc ctggctcacc ctitcttcca ggtatgttcc aagccagttt cccatctcg
1081 actctgtatag ctttcttggaa gccccccagcc ctaatctcac ctctctcc agtgtgggt
1141 tgaccaggct tgcgttggg ctatttggac tcaggtggc cctctgaact tgccttaaac
1201 actcaccttc tagtcttggc cagccaaactc tgggaataca ggggtgaaag gggggaaacc
1261 gtggaaatgtt aagggaaatgtt cagtttgc tgcacttaag ttgccttcca ccacccttc
1321 cccctctct tagttatttgc tgaagagggt tggtataaaa atattttaaa aaaagccctt
1381 ctacacgttta gatttgcgtt accaatctctt gaatggccca taattttat ttccagtt
1441 tggatgttcc accatccaa gcttgcgtt gcccacaatgtt tataaaaggc caaatgtatag
1501 cggggggctaa ttgggtgtt ttggaaacca agttaaaacaa aaccactggg aggagtctat
1561 tttaaaaatgtt tgggtgttggaa aaaatagatc caatcgtttt atacccttgtt tagtgtttt
1621 ctcacccatccaa taggtgggaaactc gactgaagac tcagccggg tggcgcaga aaaaatgtt
1681 gccccagttcc ctttgcgtt cccttctaca ggcattttttt ggcattttttt ggcattttttt
1741 gggattgttcc ttcatccaa tctattgtt caccatggcc ttatggggca ggttggggat
1801 gtttgcgtt cccttcttcc tttagtatttgc tttagtgc tttttttttt gatccctgtt
1861 cccatccatccaa taggtgggaaactc gactgaagac tcagccggg tggcgcaga aaaaatgtt
1921 tcatttttgc aatgttgcata ctttttgcgtt gcttgcgtt gttttttttt gttttttttt
1981 tttttttttttaaaatgtt tttttttttttaaaatgtt tttttttttttaaaatgtt
2041 agttggcgtt tttttttttt tttttttttttaaaatgtt tttttttttttaaaatgtt
2101 ggggtttttgtt aatgttgcata cttttttttttaaaatgtt tttttttttttaaaatgtt
2161 acccttgcgttcc tttagtgcgtt cttttttttttaaaatgtt tttttttttttaaaatgtt

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M74091 Human Cyclin C

1 gagcgcgggtt accggacggg ctgggtctat ggtcgctcc cgccgcgtcc gccgcgtgg
61 gcttttttat cagggcaagc tggttccat ggcaggaaac tttggcaga gctccacta
121 ttgtcatgg atttggata aacaagatct gtgtaggag cgccaaaagg atttaaagt
181 tcttcagag gaagaatatt ggaagtata aatattttt acaaatgtt tccaagcatt
241 aggtgaacat cttaaatata gacaacaagt tattgccact gctacggat attcaagag
301 attctatgcc aggtattctc tggaaagtat agatcctgtt taatggctc ctatcatgtt
361 gttttggca tccaaagttag aggaatttgg agtagttca aatacaagat tgattgtgc
421 tgctacttct gtattaaaaa ctagatttc atatgcctt ccaaaggaat ttccattatag
481 gatgaatcat atattagaat gtgaattcta tctgttagaa ctaatggatt gtgttgtat
541 agtgtatcat cttatagac ctttgctcca gtatgtgcag gacatggcc aagaagacat
601 gtgtgttccc ctgcatttgc ggatagtgaa tgatactac agaacgcgtc ttgcctact
661 gtatccctct ttcatgtat ctttagcttgc cttatgttgc gcctgtgtt tacagcagaa
721 agatggcagg caatggtttgc tggatgttgc tggatgttgc gaaaagattt tggaataat
781 cagggttattttaaaactat atgagcagtgc gaagaatttgc gatgagagaaa aagagatgg
841 aaccattctt agtaagatgc caaaacccaa accacatccaa aacagtgttgc gagagcagg
901 tccaaatggaa agtcagaact ctagctacat ccaatcttta aacattccgtt agaattccat
961 agtggaccac ttggaaataa accattggac agatttcgtt aatgtcttca ttggaaacaca
1021 aatgaaaatgt aatagcttgc ttctgtcaag cataattggaa agtgttttgc aaaa
1081 tagttttctt ttaataatgtat tctgtatcat aattgttgc ttaatcttgc tgattataaa
1141 tggtggaaa ggttctaaagg ggacccatag acagacatcat atagacattt caaaattat
1201 agctttgtat tagtataata ttctttaatttggataataa aatattgttgc tttttattaa
1261 gccaggaaac atgaagcata atttggat aattcttgc ggtcattttgc ggacccaaaa
1321 aggacgtaaa attacatgtc aatctatgttgc ggttttttgc cttccataat ttaacttta
1381 aaactgttatt taaggaatca aatcttacaa aatcttgc gatgttgc ttttttttttgc
1441 taatttcagg gaaattaatc aagtaccgtt aatgttgc ttttttttttgc
1501 gtttgagg

Figure 24. (Page 13 of 46)U60325 Human DNA polymerase gamma

1 aggatttggg gtggaaggca ggcatggta acccatgtca ctgacaggag agcagagaca
61 gacgtgtctc ttcacacgtc ttccagccag taaaagaagc caagctggag cccaaagcca
121 ggtgttctga ctcccacgcgt gggggccct gcaccaacca tgagccgcct gctctggagg
181 aagggtggccg ggcacccgt cggccaggcg cgggttccag ctccggggcg ctgggtctcc
241 agctccgtcc cgcgtccga ccccagcgcac gggcagcggc ggccgcagca gcagcagcag
301 cagcagcagc acgagcaaca gcagccctcag cagcccaag tgctatccctc ggagggcggg
361 cagctgcgc acaacccatt ggacatccag atgctctga gagggctgca cgagcaaact
421 ttcgggcaag gaggggagat gcctggcag gccgcggcgc gcccgcacgt cgagcacctg
481 cagaagcacg ggctctgggg gcagccagcc gtgccttgc cccagctgga gctgcgcctg
541 ccgcctctc acggggacaa cctggaccag cactccgc tctggccca gaagcagagc
601 ctgccttacc tggaggcggc caacttgcgt tgcaaggccc agctccccca gaagccccc
661 gcttggccct gggggaggg ctggaccggc tacggccccc agggggagggc ctgatccctg
721 gccatccccc aggagcgggc cctgggttc gacgtggagg tctgcttgc agaggaaact
781 tgcccccacat tgggggtggc catatcccc tcggccttgtt attcctggtg cagccagcgg
841 ctgggtgaag agcgttactc tggaccagc cagctgtgc cggctgacct catccccc
901 gaggtcccta ctgggccag cagcccccacc cagagagact ggcaggagca tttagtggtg
961 gggcacaatg ttcccttga ccgagctcat atcaggggac agtacctgtt ccagggtcc
1021 cgcacatgcgtt tccctggacac catgagcatg cacatggca tctcagggtt aagcagcttc
1081 cagcgcagtc tggatagc agccaaggcag ggcaaacaca aggtccagcc ccccacaaag
1141 caaggccaga agtcccagag gaaagccaga agaggcccag cgcacatc tctggactgg
1201 ctggacatca gcagtgtcaa cagtctggca gaggtgcaca gactttatgt agggggccct
1261 cccttagaga aggacccctcg agaactgttt gtgaaggggca ccatgaagga cattcgttag
1321 aactccagg acctgatgc ttaactgtgc caggacgtgtt gggccaccca tgaggtttc
1381 cagcagcagc taccgcctt ctggagagg tgcctccacc cagtacttgc ggcggccatg
1441 ctggagatgg gtgtctcta ctcgcctgc aaccagaact gggagcgtt cttggcagag
1501 gcacaggcata cttatgagga gtcacccggg gagatgaaga agtctgtat ggatctggcc
1561 aatgtgcctt gccagctgtc ttcaggagag aggtacaaag aagacccctg tctctgggac
1621 ctggagtggg acctgcaga attaagcag aagaaagctt agaagggtt gaaaggaaacca
1681 gcccacccca gcaagttgcc catcgagggg gctggggccc ctgggtatcc catggatcag
1741 gaagacccctcg gcccctgcag tgaggaggag gagttcaac aagatgtcat ggcggccgc
1801 tgcttgcaga agtgcagggg gaccacagag ctccctggca agcggccca gcaacccct
1861 ggacacccctg gatggatccg gaagctctgc cccggctttag acgcacccctgc atggaccc
1921 gcccacccca tcctcaggctt gcacatgcgg gtcacacca aactcatggc acttaccc
1981 gatggctcc ctctgeacta ctcagagctgtt catggctgg gctacttggt gcctgggg
2041 cgggacaacc tgcccaagctt gcccacaggaccaccctgg agtcagctgg ggtggctgc
2101 ccctacacccatccatccatccatccatccatccatccatccatccatccatccatccatccat
2161 ctgtatccatccatccatccatccatccatccatccatccatccatccatccatccatccatccat
2221 tggcaaaacgg tagaagaact ggattacttta gaagtggagg ctgaggccaa gatggagaac
2281 ttgcgagctg cagtgcagg tcaaccccta gctctgtactg cccgtggcgg ccccaaggac
2341 acccagccca gctatccatccatccatccatccatccatccatccatccatccatccatccat
2401 tggttttca agtgcctca caaggatggt aatagctgtatgtggaaag ccccttgc
2461 aaggacttcc tgcccaagat ggaggatggc accctgcagg ctggcccaagg aggtgc
2521 gggccccctgt ctctggaaat caacaaaatg atttcttcttggaggaacgc ccataaacgt
2581 atcagctccc agatgggtt gtggctgccc aggtcagtc tgcctggcgtc tgcctggc
2641 caccctgcact atgatgagga aggcccttat gggccatcc tgccttgc ggtgactg
2701 ggcaccatca ctgcggggc tggagccca acatggctca cccgcagcaaa tgccggcc
2761 gaccgagtagt gcaatggcgtt gaaagccatg gtgcaggccc cacctggctca cacccttgc

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2821 ggtgctgatg tggactccca agagctgtgg attgcagctg tgcttgaga cgcccaactt
2881 gccggcatgc atggctgcac agccttggg tggatgacac tgcagggcag gaagagcagg
2941 ggcactgatc tacacagtaa gacagccact actgtggca tcagccgtga gcatgccaaa
3001 atcttcaact acggccgeat ctatggtgc gggcagccct ttgctgagcg cttactaatg
3061 cagttAAC accggctcac acagcaggag gcagctgaga aggcccagca gatgtacgct
3121 gccaccaagg gcctccgctg gtatcggtcg tcggatgagg gcgaggtggct ggtgagggag
3181 ttgaacctcc cagtggacag gactgagggt ggctggattt ccctgcagga tctgcgcaag
3241 gtccagagag aaactgeaag gaagtcaacag tggagaagg gggaggtgg tgcgtacgg
3301 gcatggaagg ggggcacaga gtcagaaatg ttcaataaagc ttgagagcat tgctacgtct
3361 gacataccac gtaccccggt gtcggctgc tgcatcagcc gagccctgga gccctcggt
3421 gtccaggaag agtttatgac cagccgtgtg aattgggtgg tacagagctc tgcttgac
3481 tacttacacc tcatgcttgt gccaatgaaag tggctgtttg aagagttgc catagatggg
3541 cgcttcgtca tcagcatcca tgacgagggt cgctacctgg tgccccgggaa ggaccgctac
3601 cgcgtcgccc tggccttgca gatcaccaac ctcttgacca ggtgcattt tgccctacaag
3661 ctgggtctga atgacttgcc ccagtcagtc gcctttca gtgcagtcga tattgaccgg
3721 tggctcaggaa aggaagtgc acatggattgt aaaacccctt ccaacccaaac tgggatggaa
3781 aggagatacg ggattccca gggtaagcg ctggatattt accagataat tgaactcacc
3841 aaaggctct tggaaaaacg aagccagect ggaccatagc actgcctgga ggctctgtat
3901 ttgcctccgt ggagcttcat cgggggtggc caggctccca aactcaggct ttcaatgt
3961 cttttgcaa aagggttgc taaggccagc cattttcag tagcaggacc tgccaaag
4021 attccttcata actgaaggtg cagttgaatt cagtgggtc agaaccaaga tgccaaacatc
4081 ggtgtggact acaggacaag gggcattgtt gcttgtgg taaaaatgaa gcagaagccc
4141 caaagttcac attaactcag gcatttcatt tatttttcc ttcttcgtt ggctgggttct
4201 ttgttcgtc cccatgctc tcatgcgtg ccctagaagg ggaaagaatt aatgcctaa
4261 cgtataaac ctgcctcaag gcagtgaaa taaaaaaaag aaaaaaaaaaaa

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X52479 Protein Kinase C alpha

1 ggagcaagag gtggttgggg ggggaccatg gctgacgtt tccgggcaa cgactccacg
61 gcgttcagg acgtggcca ccgcgtcggc cgcaaaaggcg cgctgaggca gaagaacgt
121 cacgaggtga aggaccacaa attcatcgg cgcttcata agcagccac ctctgcagc
181 cactgcaccc acttcatactg ggggttggg aaacaaggct tcacagtgc aagtgtctg
241 ttgtggtcc acaagaggtg ccatgaattt gttaactttt ctgtccggg tgccggataag
301 ggacccgaca ctgatgaccc caggagaag cacaagtca aaatccacac ttacgaaac
361 cccacccctc gcatcactg tgggtactg ctctatggac ttatccatca agggatgaaa
421 tgtgacaccc gcatatgaa cggtcacaag caatgcgtca tcaatgtccc cagccctgc
481 ggaatggatc acactgagaa gagggggcg atttacctaaggctgagggt tgctgtatgaa
541 aagctccatg tcacagtacg agatcaaaa aatctaattcc ctatggatcc aaacgggctt
601 tcagatcatt atgtgaagttt gaaacttatt cctgatccca agaatgaaag caagaaaaaa
661 accaaaaacca tccgctccac actaaatccg cagtggaaatg agtcccttac attcaaattg
721 aaaccttcag acaaagaccc acgactgtt gttagaaatctt gggacttggg tcaacaaca
781 aggaatgact tcatggatc ctttcctt ggagtttggg agctgtatgaa gatggccggcc
841 agtggatggt acaagggttct taaccaagaa gaagggtgagg actacaacgt acccattccg
901 gaaggggacg aggaaggaaa catggaaactc aggccagaaat tcgagaaagc caaacttggc
961 cctctggca acaaagtcat cagtcctt gaagacagga aacaacccca caacaaccc
1021 gaccgagtga aactcacgga ctcaatttc ctcatggtgt tggaaaggg gagtttgg
1081 aagggtatgc ttggcgacag gaagggcaca gaagaactgt atgcaatcaa aatcctgaag
1141 aaggatgtgg tgattcagga tgatgacgtg gagtgcacca tggtagaaaa gcgactctg
1201 gccctgttg acaaaccctt gttctgacg cagctgcact cctgttcca gacagtggat
1261 cgctgtact tcgtcatgga atatgtcaac ggtggggacc tcatgtacca cattcagcaa
1321 gtaggaaaat ttaaggaacc acaaggacta ttctatgcgg cagagatttc catggatttgc
1381 ttcttcctt ataaaaagagg aatcatttat agggatctg agttgatata cgtcatgtt
1441 gattcagaag gacatataa aattgtgtt gttggatgt gcaaggaaaca catgtggat
1501 ggagtacgca ccaggaccctt ctgtggact ccagattata tcgccccaga gataatcgct
1561 tattcagccgt atggaaaatc tggacttgg tggccctatg gctgttgcgtt gtatgaaatg
1621 ctggccgggc agcctccatt tgatggtaa gatgaagacg agtatttca gtctatcatg
1681 gggcacaacg ttccatatcc aaaatccctt tccaaggagg ctgtttctat ctgc当地
1741 ctgtatgacca aacaccacg caagcggctg ggctgtgggc ctgagggggg gaggacgt
1801 agagagcatg ctttcctccg gaggatcgac tggaaaac tggagaacag ggagatccag
1861 ccaccattca agccaaatgtt gttggcaaa ggagcagaga acttgcacaa ttcttcaca
1921 cgaggacacg cctgttacaccacgtt cttgttgcgtt ttgtatgatcat agaccatgt
1981 gatttgaag gttctcgta tgcaaccc cttgttgc accccatctt acagatgtca
2041 gtatgaaact caccagcggag aacaaacacc tcccccagccccc ccagccctcc cccggacttgg
2101 agtgaatctt taaccctaaa attttaaggc cacggctgtt gctgtatcc atatggaggc
2161 ctgaaaatttgggtttagtggatctt gatcaactg ttcagggttcttcttccatca
2221 accaagaaca ttatcttagt ggaag

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D00017 Lipocortin II/Annexin A2

1 catttgggga cgctctcagc ttcggcgca cggcccagct tccttcaaaa tgtctactgt
61 tcacgaaatc ctgtgcagaagc tcagcttggaa gggtgatcac tctacacccca caagtgcata
121 tgggtctgtc aaaggctata ctaactttga tgctgagcgg gatgtttga acattgaaac
181 agccatcaag accaaagggtg tggatgaggtt caccattgtc aacatttga ccaaccgcag
241 caatgcacag agacaggata ttgccctcgcc ctaccagaga aggacaaaaa aggaacttgc
301 atcagcactg aagtgcggcct tatctggcca cctggagacg gtgatttgg gccttattgaa
361 gacacctgct cagttatgacg ctctcgatctt aaaaacttcc atgaaggggc tgggaaaccga
421 cgaggactct ctcatttggaa tcatctgcctc cagaacccaaac caggagctgc agggaaattaa
481 cagagtctac aaggaaatgt acaagactga tctggagaag gacatttattt cggacacatc
541 tggtgacttc cgcaagctga tgggtgcctt ggcaaagggtt agaaggagcag aggtatggctc
601 tgtcaattgtatgaaactga ttgaccaaga tgctggggat ctctatgacg ctggagtgaa
661 gagaaagga actgtatgttc ccaagtggat cagcatcatg accgagcggg gcgtgcggcca
721 cctccagaaaa gtatttgata ggtacaagag ttacagccct tatgacatgt tggaaagcat
781 cagaaagag gttaaaggag acctggaaaaa tgcttcctg aaccctgggtc agtgcattca
841 gaacaagccc ctgtattttg ctgatcggtt gtatgactcc atgaaggggca aggggacgcg
901 agataagggtc ctgatcggaa tcatggctc ccgcagtggaa gtggacatgt tgaaaatttag
961 gtctgaattc aagagaaagt acggcaagtc cctgtactat tataatccacg aagacactaa
1021 gggcgactac cagaaagcgc tgctgtaccc tgggtggaa gatgactgaa gccccacacg
1081 gcctgagcgtt ccagaaatgg tgctcaccat gttccagct aacaggctta gaaaaccacg
1141 ttgcgaataa cagtccccgtt ggccatccctt gtgagggtga cgttagcattt acccccaacc
1201 tcatttttgt tgcttaagca ttgcctggcc ttctgtcta gtcttcctg taagccaaag
1261 aaatgaacat tccaaggagt tggaaagtggaa gtctatgatg tgaaacactt tgccctctgt
1321 gtactgtgtc ataaaacagat gaataaaactg aattttgtact tt

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AF531293 Histone H2b, member R

1 aagagcgagt cttggcctta gcgcggcgtt tgccctccgt ctgccacgt ccagacatag
61 cgagcgcaac tcactacgag caaccacaaa gtgaacggga aaggcggcgc tttttataaa
121 cactattggg cgcaaaaag aagacgtgtt gtgggttagg gctgcagttt aattcaacc
181 aatagtagtg cgtcttcgtt atttgcgaat cctgattggg cagacctgac ctctgacgtt
241 accctgaata actaccaatc agacacaaga ctcaactct tcacccattt tgccataagcg
301 attctatata aaagcgcctt gtcataccct getcacgcgtt tttttccctt tgggtggcgc
361 tttagtgcata cacagtgcata tgccagagcc agcgaagtct gtcggccccc cgaaaaaggg
421 ctccaagaag gcgggtgacta aggccgagaa gaaagacggc aagaagcgca agcgcagccg
481 caaggagacg tattccatct atgtgtacaa gggtctgaag cagggtccacc ctgacaccgg
541 catttgcgtcc aaggccatgg gcatcatgaa ttctgttgc aacgcacattt tcgagcgcatt
601 cgcagggtgag gctcccgcc tggcgcattt caacaagcgc tcgaccatca cctccaggaa
661 gatccagacg gccgtgcgc tgctgctcc tggggagttt gccaagcagc cgggtgtccga
721 gggtaactaag gccgtcaccatc agtacaccag cgctaagttt acagtgttgtt ggttgcac
781 tctcaaccct aacggcgtttt ttaagagccca cccatgtttt caaagaaaaga gctgggtc
841 gtattccctc tctgtggcc actgacaaac cttgttaact tgctactgtt tttttgttc
901 tgaagtagag cagttattt actaatccctt agtgcattttt tttttttaga tctgccatcc
961 taatctttaga gtaagtagaag gagatggaa attttctattt ataagttcga aaccaattaa
1021 aatacgttag aaaccaatta aaatactcgtt cgggtccccgg tgggttagtgg atttggaaaca
1081 gtgcacatgtt gacgcgggtt tcagtttgcata tttggccccc caacggccgc cttccct

Figure 24. (Page 18 of 46)**NM_001657 Homo Sapiens amphiregulin**

1 agacgttcgc acacctgggt gccagcgccc cagaggtccc gggacagccc gagggcgcgc
61 gccccggcc ccagactccc caagccctcg agagcggcgc acactcccg tctccactcg
121 ctcttccaac acccgctcg tttggcggca gtcgtgtcc cagagaccga gttgccccag
181 agaccgagac gcccggctg cgaaggacca atgagagccc cgctgctacc gccggcgccg
241 gtgggtctgt cgctcttgat actcggctca ggccattatg ctgctggatt ggaccta
301 gacacctact ctggaaagcg tgaaccattt tctggggacc acagtgcgtga tggatttgag
361 gttaccta gaagttagat gtcctcagg agtgagattt cccctgttag tgaaatgc
421 tcttagtagt aaccgtcctc gggagccgac tatgactact cagaagagta tgataacgaa
481 ccacaaatac ctggctatat tgcgtatgat tcagtcagag ttgaacagg agttaagccc
541 ccccaaaaca agacggaaag tggaaaatact tcagataaac cccaaagaaaa gaaaaaggaa
601 ggcaaaaatg gaaaaaaatag aagaaacaga aagaagaaaa atccatgtaa tgcagaattt
661 caaaaattct gcattcacgg agaatgcaaa tatatagagc acctggaagc agtaacatgc
721 aaatgcacg aagaataattt cggtaacgg tggggggaaa agtccatgaa aactcacagc
781 atgattgaca gtatgttata aaaaattgc ttgcgcattt tagctgcattt tatgtctgt
841 gtgatccca cagctgtgc ttgttattaca gtccagctt gaagacaata cgtcaggaaa
901 tatgaaggag aagctgagga acgaaagaaaa cttcgacaag agaatggaaa tgtacatgct
961 atagcataac tgaagataaa attacaggat atcacattgg agtcaactgcc aagtcatagc
1021 cataaaatgtat gagtcggtcc tcttccagt ggatcataag acaatggacc cttttgtt
1081 ttagttttttaaaatccaa ttgtcactttt ttatgttata aaggtgcacg
1141 aaggtaaaaaa gtattttca aagttgtaaa taattttttaat aatatttaat ggaagtgtat
1201 ttattttaca gctcattaaa cttttaac caaacagaaaa aaaaaaaaaa aaaaaaaaaa
1261 aaaaaaaaaaa

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M90357 Human basic transcription factor 3

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2821 tcatgaggct tccaagaatg aggcaaactg aattgagtc actgtgaag ataaaacctg
2881 aagaagtta ctgggagctg ctatttata ttatgactgc tttaagaa aattttgtt
2941 tatggatctg ataaaatcta gatcttaat atttttaagc ccaagccct tggacactgc
3001 agctcttc agttttgct tatacacaat tcatttttg cagctaatta agccgaagaa
3061 gcctggaaat caagttgaa acaaagatta ataaagtct ttgcctagt atacagttt
3121 atttttat ttatgacac cgatctgtac acagtaaaaa aaatgccta tagaaagcta
3181 atcatggcat gtaatatggc tgataacctt tgaaatttga ttaaagattt aaaatcacgg
3241 tgtaagtgt acaaagggtgg tataaagttc tcaggttga aaactttgtc tccaacagtc
3301 cttatgtcct ccatgattta tatgggggt gtaaatgtg gaatagagta ttcccttagtg
3361 gataaacaga catttccttcc tgatattctc tattgtaaatgc atatgttaag tgccttttat
3421 gaattaccct cggtgttatac ttcccttattt cctcaatttg tgaagaacta atagctccat
3481 tttagatg taaccgtgagg tttagaactt ctaaaaagta aaagtaatct ccagatccct
3541 tctttgtagg atattttata aggtgacttg gaaaaggtag tgtagaaat aggagtggct
3601 cctgggtcat tgtctttcc ttaatgtta cacctaataa atgaataggg ttatgtttt
3661 atttaataaa aaatatacag taaaatttag catatacagt taaaagaatt tataatgtct
3721 gccactataa ccaggcttac cagacagttt catggccag aaaatcccta aacatagggt
3781 tactttaaa catttacaa attacaatgtt aacaatgtt taatctgaac caaggccatt
3841 tgaggagaaa tagtctact tgtaggtat ttattttaa attttcata gcaatttgca
3901 agtaccctttt gaaagtattt tcagttgtat ctaaaaatgtca ctattaaccg tgg

Figure 24. (Page 21 of 46)**NM 006219 Homo sapiens phosphoinositide-3-kinase, p110 subunit**

1 atgtgcttca gttcataat gcctcctgct atggcagaca tccttgacat ctggcggtg
61 gattcacaga tagcatctga tggctccata cctgtggatt tcctttgcc cactgggatt
121 tatatccagt tggaggtacc tcgggaagct accatttcatt atattaagca gatgttatgg
181 aagcaaggta cacaattaccc aatgtcaac ctccttatgg atattgactc ctatatgtt
241 gcatgtgtga atcagactgc tgatatatgg gagcttgaag atgaaacacg aagacttgt
301 gatgtcagac ctttcttc agttctaaa ttatgtacaa gaagttgtga cccagggaa
361 aaatttagact caaaaaattgg agtccctata gaaaaaggta tgcatgaatt tgattcctg
421 aaggatcctg aagtaaatga atttcaaga aaaaatgcgc aattcagcga ggaaaaaaatc
481 ctgtcacttg tgggattgtc ttggatggac tggctaaaac aaacatatcc accagagcat
541 gaaccatcca tccctgaaaaa cttagaagat aaactttatg ggggaaagct catcgttagct
601 gttcattttg aaaactgcca ggacgtgtt agtttcaag tgcattctaa tatgaatcct
661 atcaaagtta atgaattggc aatccaaaaa cgittgacta ttcatgggaa ggaagatgaa
721 gttagccccct atgattatgt gttcaagtc agcgggagag tagaatatgt ttttggat
781 catccactaa ttcaatccca gtatatccgg aactgtgtga tgaacagagc cctgccccat
841 ttatacttg tggaaatgtcg caagatcaag aaaatgtatg aacaagaat gattgccata
901 gagggctgcca taaatcgaaa ttcatctaat cttccttcattaccacc aaagaaaaaca
961 cgaattattt ctcatgttg ggaaaataac aacccttccaaattgtctt ggttaaggga
1021 aataaaactta acacagagga aactgtaaaaa gttcatgtca gggctggct tttcatgg
1081 actgagctcc tggtaaaaac catcgtaaac tcagaggat cagggaaaaa tgatcatatt
1141 tggaaatgaac cactggaatt tgatattat atttgtact taccaagaat ggctcgatta
1201 tggatggctg tttatgcattttggataaa gtaaaaacga agaaatcaac gaaaactatt
1261 aatccctcta aatatcagac catcaggaaa gttggaaaag tgcattatcc tggatgtgg
1321 gtaaaatcgaa tggtttga ctttaagga caattgagaa ctggagacat aatattacac
1381 agctggctt cattccctga tgaactcgaa gaaatgtga atccaatggg aactgttcaa
1441 acaaatccat atactgaaaaa tgcacacgtt ttcatgtta aatttccaga gaataaaaaaa
1501 caaccitattt attaccctcc cttcgataag attatgaaa aggcatgtga gattgcaac
1561 agtgatgtg ctaatgtgc aagtcgaggt ggaaaaaaatgt ttcttcctgtt attgaaagaa
1621 atcttggaca gggatcccctt gtcactgtc tggaaaatg aatggatct tatttggact
1681 ttgcgacaag actgcccaga gattttccca caatctgtc caaaattact gctgtcaatc
1741 aagtggata aacttgagga tggatgtcgat cttcaggcgc tgcttcagat tggcctaaa
1801 ctggcccccc gggaggccctt agagcttcgtt gatttcaact atccagacca gtacgtcga
1861 gaatatgtcg taggtcgctt ggcacagatg agtgtatgaa aactttctca atatcttta
1921 caactggatc aagtgtaaa atatgacgtt ttcttcgtt gtccttcctc tagattccct
1981 ttggaaagag cacttggtaa tcggaggata gggcagtttc tattttggca tcttaggtca
2041 gaagtgcaca ttctgtgtt ctcgtacaa ttgggtgtca tccttgaaagc atactgcccgg
2101 ggaagtgtgg ggcacatgaa agtgcatttc aagcagggtt aagcactcaa taatggaaaa
2161 actttaataa gttaatcaa actgaatgcc gtgaagttaa acagagccaa aggaaaggag
2221 gccatgcata cctgttaaa acagagtgtt taccgggaag ccctctgtca cctgcagtca
2281 cccctgaacc catgtgtt ctcgtacaa ctctatgttggaaaatgtcaaa atacatggat
2341 tccaaatgaa agccctgtg gctggatatac aataacaagg tattttggtaa ggattcgtt
2401 ggagtgattt taaaatgg tttatgttta cggacaggata tggatgtt cccaaatgtt
2461 cgcttgcatttgg atttactctg gaaagaagct ggtttggatc ttggatgtt gccttgc
2521 tggatgttcaaa caggagatcg ctctggccctt attgaagttt tgacgttgc tggacacatt
2581 gctgacatcc agtgcacacg tagcaatgtg gctgctgcag cagcctcaa caaagatgcc
2641 ctctgtcaact ggcttaaaga atacaactctt gggatgacc tggacccgagc cattgaggaa
2701 ttatcactgt cctgtgtt cttcttgcgtt gcttgcatttgc tttttggat tggatgttgc

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2761 catagtgaca acatcatggt caaaaaaaact ggccagctct tccacattga ctttggacat
2821 attcttgaa attcaaatac taagttggc attaaaagg agcgagtgcc ttttattctt
2881 acctatgatt tcattcatgt cattcaacaa gaaaaaacag gaaatacaga aaagttggc
2941 cggttccgc agtgttgta ggatgcatat ctgattttac gacggcatgg gaatcttc
3001 atactctct ttgcgcgtat gttgactgca gggcttcctg aactcacatc agtcaaagat
3061 atacagtatc ttaaggactc tctgcatta ggaaagagatg aagaagaagc actcaaacag
3121 ttaagcaaa aatttgtatga ggcgctcagg gaaagctgga ctactaaagt gaactggatg
3181 gcccacacag ttccggaaaga ctacagatct taa

Figure 24. (Page 23 of 46)**X04412 Human Gelsolin**

1 gccgtgtcgc caccatggct ccgcacccgc ccgcgcggc gctgcttgc ggcgtgtccc
61 tggcgctgtc cgccgtgtc ctggccgtcc gcgccggcac tgctcgccgg gggcggtccc
121 aggccccggc gccccagggg cgggtgcggc aggccggcc caacagcatg gtgggtggaaac
181 acccccgagtt cctcaaggca gggaaaggagc ctggccgtca gatctggcgt gtggagaagt
241 tcgatctggt gcccgtgccc accaaccctt atggagactt ctgcacggc gacgcctacg
301 tcatactgaa gacagtgcag ctgaggaacg gaaaatctgca gtatgaccc cactactggc
361 tgggcaatga gtgcagccag gatgagagcg gggccggc catcttacc gtgcagctgg
421 atgactacct gaacggccgg gccgtgcagc accgtgaggt ccaggcgctt gagtcggcca
481 ctttccttagg ctacttcaag tctggcctga agtacaagaa aggagggtgtg gcatcaggat
541 tcaaggcacgt ggtiaccacac gaggtgttgc tgcaagact ctccaggc aaaggccggc
601 gtgtgttgc tgccaccggag gtacctgtt cctgggagag cttaacaat ggcgactgct
661 tcatactgga cctggcaac aacatccacc agtgggttgc ttccaacacg aatcggtatg
721 aaagactgaa ggccacacag gtgtccaagg gcatccggg caacgagccg agtggccggg
781 cccgagtgca cgtgtctgag gagggcactg agcccgaggc gatgtccag gtgtgggcc
841 ccaagccggc tctgcctgca ggtaccggagg acaccgc当地 ggaggatgccc gccaaccgc当地
901 agctggccaa gctctacaag gtctccaatg gtgcaggac catgtccgtc tccctcgtgg
961 ctgtatgagaa ccccttcgccc cagggggccc tgaagtca gggactgttcc atcctggacc
1021 acggcaaaga tggaaaatc ttgtctgga aaggcaagca ggcaaaacacg gaggagagga
1081 aggctgcctt caaaacagcc tctgacttca tcaccaagat ggactacccc aagcagactc
1141 aggtctcggt ctttcctgag ggcgggtgaga ccccaactgtt caagcagttc ttcaagaact
1201 ggcgggaccc agaccagaca gatggcctgg gcttgcctta ctttcaggc catatgc当地
1261 acgtggagcg ggtgccttc gacgc当地ccca ccctgc当地ac ctccactgccc atggccggcc
1321 agcacggcat ggtatgacat ggc当地aggcc agaaacagat ctggagaatc gaagggttca
1381 acaagggtgccc cgtggaccct gccc当地atg gacagttca tggagggagc agtacatca
1441 ttctgtacaa ctaccgc当地 ggtggccgccc agggccagat aatcttac tggcagggtt
1501 cccagttac ccaggatgag gtcgctgcat ctggccatct gactgcttag ctggatgagg
1561 agctgggagg tacccctgtc cagagccgtg ttgtccaagg caaggaggccc gccc当地ctca
1621 tgaggctgtt tggggaaag cccatgatca tctacaagg cggcacccctc cgc当地ggc
1681 ggc当地acagc ccctgccc当地 acccccttcc tccaggctgg cggccaaacagc gctggagcc
1741 cccggctgt tgaggatttgc tctaaggctg gtgcactgaa ctccaacatg gccc当地tgc当地
1801 tggaaaacccc ctacccgttcc tacctgtggg tgggtacagg agccagcgag gcaagagaaga
1861 cggggccca ggagctgctc agggtgtc gggccaaacc tggcagggtg gcaaggca
1921 gcgagccaga tggctctgg gaggccctgg gcgccaggc tgc当地accgc acatccccac
1981 ggctgaagga caagaagatg gatgccc当地 ctccctgc当地 ctggc当地tgc当地 tccaacaaga
2041 ttggacgttt tggatgatca gagggttgc当地 tgagctcat gc当地ggaaagac ctggcaacagg
2101 atgacgtcat gcttctggac acctgggacc aggttttgc当地 ctgggttgc当地 aaggattctc
2161 aagaagaaga aaagacagaa gcttgactt ctgctaaaggc gtacatcgag acggaccagg
2221 ccaatcgccg tggccggc当地 cccatcaccg tggtaagca aggcttgc当地 cttccctt
2281 ttgtggctg tttcttggc tgggtatgatttgc当地 tggcaggccc ttggacagg
2341 ccatggctga gctggctgccc tgaggagggg caggccccc当地 ccatgtcacc ggtcactgccc
2401 ttgtggact gtc当地ccctt caaagaggcc ttagagcgag cagagcact ctgctatgag
2461 tggatgatca gggatgatca tgggttgc当地 tggcaggccc ttggacagg
2521 gcaaaaattc agatgcttgc当地 caaaaatttgc当地 taaaatgtca gtttggaa attaaatcc
2581 aataaaaaaca ttgtggact tg

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NM_001759 Homo sapiens Cyclin D2

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2821 ttttttttgcgctgctaa gaagctaaag tcatccatcc ttattcacgt tgacagtacc
2881 tagctgtat gtttcacaga gtgtgctgct atttataaa cattttata atatatttt
2941 ttactgctta aattccaagt cctgaagtag atgggtgaga tatgagttct tcgtactgga
3001 aaagcccttc cgtagttgt ttcttctgg tagcatattc atgggtgtt tttttttct
3061 ttttggttt ttgggtttt ttttttcct ctgatcacat tcitcaaaga cggagtttt
3121 ttacccctcg gtttactgga caaaaatcaat aactacaaaaa ggcaatgatt cacgctttg
3181 tttcataat acctcacaac cgtacagttt ctgcttggga gcccattcgc atgaggaata
3241 cagaaggcgt gtgagcagggg ctgactccct ctcagggtgga aggccccggc gtcactcc
3301 caggacctt ttggcatg gaggccatcg ggctccca gtagaccctgg tattccatc
3361 atgatggaaa aaatacattt aaccaaggga tcctccctcc cctcaaggc agacgttcag
3421 tacaaacatt tatgcggtag getcagatgt cgtaatttgc acttaggtac caggtgtcag
3481 gaaacagact aaaagaattt ccaccaggct gtttggagat ctcatacttgg gagcttttc
3541 aaaagcccccccttccatctgc aaaggccctt tcatacttga agttttccctt ctcggcttt
3601 cccctccctt ggcattggaca ctttgtttt aggatcatct ctgcagggtt ctaggtctg
3661 aatctgcgag tagatgaacc tgcaaggc acgcgtttatg tgcttcctt ctccctcc
3721 tgtctcaaacc tgccgaggca agcactatgc aagccccaggc cctctgtga gggactaa
3781 acggcgggttcaatcac actgaatttg caggataaga aaaataggc agataagtt
3841 gggatgatag ttgaaggaggtt gtaagaggc tgcttctcta cagagggtgaa attccagatg
3901 agtcgttcc ttggaaatgt tgtagaaagggc ttgtcaggac ttgtgagttt agcatgaccc
3961 taaaattcttta gggatttttctt ggtgggacaat tgggtgttga atttgaagt ttggagagg
4021 gaatggggc agccagcaag taagcttagcc agatgtttctt caagagccag ctgtctcg
4081 cacactctcc ttggcccccaaa ggagtcccac ggaatggggaa aatggggaaac ccgtggagtc
4141 ttggaaatctt tggggctaa agagaaaccc aggtgcaat tcatttcatg gtgactgacc
4201 cttagcttta aacagaagca gcaaatgaaa gaacccggaca aataaggaag ggcacaagcc
4261 taccggactt tatttacagt ctgtaactttt ccactcttcc tgcgttcccg aggccccctgg
4321 gtcctcttag ctttcttccatctt gggcccttgc tgatgtatgg gtgtggggct
4381 gccgatggga aagtcccccccttcttgc ttgttaggctt ctctgttta aacacaagaa
4441 ggaatcccttggggatcttcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat
4501 gaggagcttccccccttggggatcttcttgc ttgttaggat ttgttaggat ttgttaggat
4561 ttttcttac ctcccactaa aggggttcca aattatcttgc ttgttaggat ttgttaggat
4621 ttgttctatcttcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat
4681 ttgtcccccaaa gctgcaaaa ttgttgcctt tccctctttt tggccaaatcttccatg
4741 gaaatcccttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
4801 cagccaagaa gcctgcagga gaaagccaag ggccgttcccttccatg
4861 tgctgagagg cgagcttccctt gaaagggggg ctgttcttccaggaggctt attttact
4921 gcctcaggac cccactggag agcacagcat gccttactac tgggtcatcc ttgttctatg
4981 tgctctgtatcttcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5041 taatgttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5101 gcaggatttttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5161 ctctccagac ttgttgcctt gggccatgg actggaaatgttgc ttgttaggat ttgttaggat
5221 agatgttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5281 tggggatcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5341 agataatatttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5401 ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5461 atagctttaa aatggggatcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5521 ctgttagctatcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5581 ctgttagctatcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5641 tacttcttgc ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat
5701 ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat ttgttaggat

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5761 gaccctattc tcggctcagg tttgagaag ccatcagcaa atgtgtacgt gcatgcgtga
5821 gctgcagcct gcatcccttc gcctgcagcc tactttgggg aaataaaatg cttactgac
5881 tgttagccatt acagtatcca atgtcttttgc acaggtgcct gtccttgaaa aacaaagttt
5941 ctattttat tttaattgg ttagtctt aactgctggc caactttac atccccagca
6001 aatcatcgaa ccattggatt tttccattt tggtcatcac ccttataatca tgtacctcag
6061 atctctctct ctctctctc tctcagttat atagtttttgc tttttttct
6121 ttctttttc ttttttttc tgcttaaaaa caagtgtat gccatatcaa gtccatgtta
6181 ttctctcaca gtgtactcta taagagggtt ggggtgttgtt tggtcagga tgtagaaag
6241 tgctgataag tagcatgatc agtgtatgcg aaaagggttt taggaagtat ggcaaaaatg
6301 ttgtattggc tatgtatggc acatgatataa gtcagctgcc tttaagagg tcttatctgt
6361 tcagttttaa gtgattttaaa aaaataataa cctgtttct gactagttta aagatggatt
6421 tgaaaatggc ttgaatgca attaggttat gctatttgaa caataaactc accttgacct

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NM 004444 Ephrin Receptor (EphB4)

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2821 gggcgagtgg ctccgggcca tcaaaatggg aagatacga aaaaatggg
2881 cttggctcc ttccgagctgg tcagccagat ctctgcttag gacccgttcc gaatcgagg
2941 cactctggcg ggacaccaga agaaaaatctt ggccagtgtc cagcacatga agtcccaggc
3001 caagccggga accccgggtg ggacaggagg accggcccg cagtaactgac ctgcagggAAC
3061 tc(ccc)cccc aggacaccg cctcccccatt ttccggggca gagtggggac tcacagaggc
3121 cccccccct gtccccccgt ggattgcact ttgagccccgt ggggtgagga gttggcaatt
3181 tggagagaca ggattttgggg gttctgccat aataggaggg gaaaatcacc cccagccac
3241 ctcggggAAC tccagaccaa gggtagggc gcctttccct caggactggg tgtgaccaga
3301 ggaaaaggaa gtcccaaca tctcccgcc tccccccgtt cc(ccc)tcac ctgtatgggt
3361 gcgttcccgcc agaccaaaga gagtgact cccttgcag ctccagatgt gggggcgtgt
3421 cccagggggc aagaagggtgtcaggggccc agtgacaaaa tcattgggt ttgtatcccc
3481 aacttgtc tgcaccacc aaactcaatc attttttcc ctgtaaatg cccctcccc
3541 agctgtgc ttcatatttga aggttttga gttttgttt tggtcttaat tttctcccc
3601 gttcccttt tggtcttcg ttttgtttt ctaccgtcct tgctataact ttgtgttgga
3661 gggAACctgt ttcactatgg ccccttgc ccaagttgaa acagggggcc atcatatgt
3721 ctgtttccag aacagtgcct tggtcatccc acatccccgg accccgccctg ggaccccaa
3781 gctgtgtcct atgaagggtgt ggggggtgag gtatgtaaaa gggcggtgt tggtgggtgg
3841 acccagaaac ggacgcccgt gcttggagggttcttaat tatattaaa aaagtaactt
3901 ttgtataaaa taaaagaaaa tgggacgtgt cccagtcac ggggt

Figure 24. (Page 29 of 46)**M18737 Human Hanukah Factor /granzyme A**

1 atgaggaact cctatagatt tctggcatcc tctctctcag ttgtcgttc tctctcgta
61 attcctgaag atgtctgiga aaaaattatt ggaggaaatg aagtaactcc tcattcaaga
121 ccctacatgg tcctacttag tcttgacaga aaaaccatct gtgctgggc ttgattgca
181 aaagactggg tggactgc agtcactgt aacttgaaca aaaggtccc ggtcattctt
241 ggggctcact caataaccag ggaagagcca acaaaccaga taatgcgtt taagaaagag
301 tttccctatc catgctatga cccagccaca cgcgaagggt accttaaact ttacagctg
361 acggaaaaag caaaaattaa caaatatgtg actatccttc atctacctaa aaagggggat
421 gatgtgaaac caggaaccat gtgccaagt gcagggtggg ggaggactca caatgtgca
481 tcttggtccg atactctgag agaagtcaat atcaccatca tagacagaaa agtctgcaat
541 gatcgaaatc actataattt taaccctgtg attggaaatg atatggttt tgctggaagc
601 ctccgaggtg gaagagactc gtgcaatgga gattctggaa gccctttttt gtgcgagggt
661 gtttccgag gggcacttc ctggccctt gaaaataat gggagaccc tcgtggccct
721 ggtgtctata ttcttctc aaagaacac ctcaactgga taattatgac tatcaaggga
781 gcagttaaa taaccgttc ctttcattta ctgtggcttc ttaatctttt caca

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NM_000551 von Hippel-Lindau tumor suppressor (VHL)

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2761 agtatgccgc tgcactccag cctggggac agagcaagac cctgcctcaa aaaaaaaaaaa
2821 aaaaaaaaaatt caggccggga atgggtttc acgcctgtaa tcccagcact ttggggggtc
2881 gaggtggca gatcacctga ggtcaggagt tcgagaccag cctggccaac atgtaaaac
2941 cccattcta ctaaaaata caagaattag ctgggtgtgg tggcgcatgc ctgtaatcct
3001 agctactcg gaggctgagg caggagaatc acttgacccc aggaggcgaat gattgcagt
3061 agctgatatc gcaccattgt actccagcct gtgtgacaga gcaatactt tgcccaaaa
3121 aaaaaaaaaa ttcaaatcg agtgaagtga atgagacact ccagtttcc ttctactccg
3181 aatttttagct ctccttca acattcaaca aatagtctt tttttttt tttttttt
3241 gggatggagt ctccccctgt tgccaggct ggagtgcaga ggtgcgatct ctgcctacta
3301 caagctctgc ctccccgagtt caagtgattc tccctggctca ccctccctgag ctgggattac
3361 aggcgcctgc caccatgcct ggctaaatttt gtgttttag tggagacggg gttcaccat
3421 gtgtccagg atggcttga tctcttgacc ttgtatcca cccaccctcag cctcccaag
3481 tggggattt acaggtgtga gccaccgcgt ccagccagct ttattttttt tttaagctg
3541 tctttgttc aaaatgatag ttcatgtctcc tcttgtaaa acctgcaggc cgagcacagt
3601 ggctcatgcc tgtaatccca gcattttggg agaccaaggc ggatggatca cctgaggta
3661 ggagctcaag accagcctgg ctaacatggt gaaacctcat ctccacttaa aatacaaaaa
3721 ttggccggccg cggccgctca tgcctgtat cccagcactt tgggaggcct aggccgggtgg
3781 atcacacgt cagggaaatcg agaccatctt ggctaaacacg ggtgaaaccc cgtcttatt
3841 aaaaaataga aaaaattagg cgggcgtgtt ggtgagcgc tgtagtccca gctactcgag
3901 agcctgaggc aggagaatgg catgaacctg gaagggtggag cttgcagtga gctgagatgg
3961 tgccactgca ctctaaccctg ggcgcacagag tgagactccg tctcaaaaaa aaaaacaaaa
4021 accaaaaactt atccagggtgt ggccgtgggc gcctgtgagg caggcgaatc tcttgaaccc
4081 gggaggcggga ggtgcagtg agcctggatc acaccattgc actccagcct gggaaacaag
4141 agtggaaattc catctaaaaa ccaaatttc aaaaaaaaaa catggccgtt ggtactgt
4201 tttttgtgt tgccttggaa aaattttttt acatggatgg ttttcattt
4261 cgaatctgtt gaaatgttta aatatatcg tcttaagaga cggtaagggtt cctatttcaa
4321 gtttttttgg ttttttttgg ttttttttttgg ttttttttttgg ttttttttttgg
4381 aaggaaatag gcagggtgtg ttgtgtgggt ttttttttttgg ttttttttttgg
4441 ttggaaacctt gtttacataa aggccaaaga tgggaaggag atccaaacat aagccaccag
4501 ctcattcca agtctcttctt ctttccaacc ctggattttt ttttttttttgg ttttttttttgg
4561 tcttttttttgg ttttttttttgg ttttttttttgg ttttttttttgg ttttttttttgg
4621 gaaaaatattt aagaagaaaaa acattcacat cggaaacaaa gttttttccc atggaaacag
4681 aaccctaaag ggtaagggtgt tagtatttca ccagcaattt tggttggaaat aaggccaggc
4741 gaggtggctc acgcctgtaa tctcagcact ttgggaggcc agggcaggca gatcatctga
4801 ggtcaggagt ttggagaccag cctggccaac atggtggaaac cctatctcta ctaaaaattt
4861 aa

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D21254 Human mRNA for OB-Cadherin-1

1 cgcggagaga tgccgccccg gcccgtcgca gcccgcgctg acttgtaat gggaccggga
61 ctggggccgg gactgacacc gcagcgcctg ccctgcgccca gggactggcg gtcggagggt
121 tgcgtccacc ctaaggccc ccagaaatca ctgtgtttc agctcagccg cccctgaca
181 ttccitcggt tgcatttg tgagtgacc aatcagatgg gtggagtggtt acagaaaat
241 tggcagcaag tatccaatgg gtgaagaaga agctaactgg ggacgtggc agccctgacg
301 tcatgagctc aaccaggcaga gacattccat ccccaagagag gtctgcgtga cgcgtccggg
361 agggcaccc cagcaagacc accgtacagt tggtggagg ggtgacagct gcattctct
421 gtgcctacca cgtaacccaa aatgaaggag aactactgtt tacaagccgc ctgggtgtgc
481 ctggcatgc tgcacag ccatgcctt gccccagagc ggcggggca ctcgcggccc
541 tcctccatg gCACCATGA gaaggcgaag gaggggcagg tgctacagcg ctccaaagcg
601 ggctggctt ggaaccagg ttcgtgata gaggagata cggggctga cccctgtct
661 gtggcaggc tcattcaga tattgactt ggtgatggg acaitaata cattctct
721 ggggaaggag ctggAACAT tttgtgatt gatgacaaat cagggAACAT tcattccacc
781 aagacgttgg atcgagaaga gagagccag tacacgttga tggcaggc ggtggacagg
841 gacccaatc ggccactgg gcccacgtg gaattcattt tcaagggttca ggacattaaat
901 gacaaccctc cggagttctt gcacgagacc tatcatgcca acgtgcctga gaggtccaaat
961 gtggAACGT cgtatattca ggtgacagct tcagatgcag atgaccccac ttatggaaat
1021 agcgcctaaat tagtgtacag ttcctcgaa ggacaaacctt attttcggg ggaagcacag
1081 acaggatca tcagaacagg cctacccaaat tggacagggg aggccaagg gggataccac
1141 gtgggtatcc agggcaaggaa catgggtggaa catatggcgg gactctcagg gacaacccaaat
1201 gtgacgatca cactgaccga tgtcaatgac aacccaccaa agttccgca gacgtatc
1261 cagatatctg tgcagaagc agccgtccctt ggggaggaag taggaagagt gaaagctaaa
1321 gatccagaca ttggggaaaaa tggcttagt acatacaata ttgttgatgg agatggat
1381 gaatcgttt aaatcacaac ggactatgaa acacaggagg ggggtataaa gctggaaaaag
1441 cctgttagatt ttggaaaccaa aagagccatat agcttgcagg tagaggcagc caacgtgcac
1501 atcgacccga agtttatcag caatggccctt tcaaggaca ctgtgaccgt caagatgc
1561 gtagaagatg ctgatgaccc cctatgttcc ttggcccaa attacatcca cgaagtccaa
1621 gaaaatgcag ctgctggcac cgtgggtggg agagtgcattt ccaaagaccc tgatgtgc
1681 aacagcccgaa taaggatttccatcgatcgtt cacactgacc tcgacagatt ttccactatt
1741 aatccagagg atggttttat taaaactaca aaaccttgg atagagagga aacagcctgg
1801 ctcaacatca ctgtcttgc acgagaaatc cacaatggc atcaggaaagc caaagtccca
1861 gtggcattt gggcccttga tgtcaacgtt aatgtccca agtttgcgtcc ctcttgc
1921 ggttcatct gtggaggttga tcagaccaag ccactttcca accagccat tggatcaatt
1981 agtgcagatg acaaggatgtt cagggccat ggaccaagat ttatcttcag cctacccctt
2041 gaaatcatccatc acaatccaaat tttcacatgc agagacaacc gagataacac acgaggcgt
2101 tacggccggc gtgggggtt cagtcggcag aagcaggact tgcacccat tggccatgt
2161 atcagcgatg cggccatccc gcccatttgc acgaccaaca ccctcaccat caaagtctgc
2221 gggcgcacg tgaacggggc actgtctcc tgcacacgc gggccatcat tctgaacgc
2281 ggcctgagca caggcccttgc gatcgcacatc ctgcctgca tgcatttgc tctggcatt
2341 gtagtattgt ttgtgaccctt gagaaggcaaa aagaaagaac cactcattgtt ctttggggaa
2401 gaagatgttcc ttgtgaccat cattacttgc gatgatgaaag ggggtggggaa agaagacaca
2461 gaagccttgc atattgcccac cctccagaat cctgtatgttcaatggatt tttcccccgc
2521 aaagacatca aacccatgttca gatcgcacatc cctggccatgtt ggcctccggc acgcccccaac
2581 agcgtggatg tcgatgactt catcaacacg agaatacagg aggacacaa tgacccac
2641 gtcctccctt atgactccat tcaatctac ggttatgttgc gggggctc agtggccggg
2701 tccctgatctt cccttagatgc gggccaccaca gattcagact tggactatgtt tttctac
2761 aactggggac ctcgtttaa gaaacttagca gatgtatgtt gttccaaaga cactttgtt

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2821 gacgattctt aacaataacg atacaatattt ggcctaaga actgtgtctg cggttcctaa
2881 gaatctagaa gatgtgtaaa caggtatttt ttaaatcaa ggaaaggctc atttaaaaca
2941 ggcaaaagttt tacagagagg atacatttaa taaaactgcg aggacatcaa agtggtaat
3001 actgtgaaat acctttctc aaaaaaggc aaatattgaa gttgtttatc aacttcgccta
3061 gaaaaaaaaa acactfgca tacaaaatat ttaagtgaag gagaagtcta acgctgaact
3121 gacaatgaag gggaaatttgtt tatgtgttat gaacatccaa gtcttcctt ttttttaagt
3181 tgtcaaagaa gttccacaa aatttagaaag gacaacagtt ctgagctgta atttcgcctt
3241 aaactctgga caactctatat gtatgtcattt ttaaacttg aaatatataa tattcagcca
3301 gcttaaaccc atacaatgtatg ttttacaatac aatgtacaat tatgtctttt gagcatcaat
3361 ctgttactg ctgattcttg taaatctttt tgcttctact ttcatcttaa actaatacgt
3421 gcccagatata actgtcttgtt ttcaagtgaga gacgccctat ttctatgtca tttttatgt
3481 atctatttgtt acaattttaa agttttttttt ttagtataca tataaatatc agtattctga
3541 catgttggaa aatgttacgg catcacactt atatttatg aacattgtac ttttgcttta
3601 atatgagctt caatataaga agcaatctttt gaaataaaaaa aagattttttt tttttttttt
3661 a

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D21255 Human mRNA for OB-cadherin-2

1 acaggcccgc gacgctcccc tcagctggcg cgccgcgcg agagatgccc cggggccgc
61 tcgcagccgc cgctgacttg tgaatggac cgggactggg gcccggactg acaccgcgc
121 gctgccctg cgccaggac tggcggctcg gaggttgcgt ccaccctaa gggccccaga
181 aatcactgtg tttcagctc acggccctg tgacattctc tgggttgc atttgttag
241 tgaccaatca gatgggttaca gaaattggca gcaagtatcc aatgggtgaa
301 gaagaagcta actggggac tggcagcc tgacgtgatg agctcaacca gcagagacat
361 tccatccaa gagaggctg cgtgacgcgt cgggaggcc accctcagca agaccaccgt
421 acagttggtg gaaggggtga cagctgcatt ctctgtgcc taccacgtaa caaaaatga
481 aggagaacta ctgttacaa gccgcctgg tggcttggg catgtgtgc cacagccatg
541 ccttgccttcc agagccgcgg gggcacctgc ggcctccctt ccatggcgc catgagaagg
601 gcaaggaggg gcagggtcta cagcgttcca acgcgtggcgt ggttggaaac cagttctcg
661 tgatagagga gtacaccggg cctgaccccg tggcttggg caggctcat tcatatattg
721 actctggtgta tggaaacatt aaatacattc tctcagggga aggagctgga accattttt
781 tgattgtga caaatcaggg aacattcatg ccaccaagac gttggatcga gaagagagag
841 cccagttacac gttgtggct caggcgggtt acagggacac caatcgccca ctggagccac
901 cgtcggaaatt cattgtcaag gtccaggaca ttaatgacaa ccctccggag ttctgcacg
961 agacctatca tgccaaacgtg cctgagggat ccaatgtggg aacgtcagta atccagggt
1021 cagcttcaga tgcaatgtac cccacttatg gaaatagcgc caagtttagt tacagtatcc
1081 tcaaggaca accctattt tgggttggaaag cacagacagg tatcatcaga acagccctac
1141 ccaacatgga cagggaggcc aaggaggagt accacgtggt gatccaggcc aaggacatgg
1201 gttggacatat gggcggactc tcagggacaa ccaaagtgc gatcacactg accgatgtca
1261 atgacaacccc accaaagttt ccgcagagcg tataccagat atctgtgtca gaagcagccg
1321 tccctgggg ggaagtagga agagtggaaag ctaaagatcc agacattggaa gaaaatggct
1381 tagtcacata caatattgtt gatggagatg gtatggaaat gtttggaaatc acaacggact
1441 atgaaacaca ggaggggggtg ataaagctga aaaagccgt agatttgaa accaaaagag
1501 cctatagctt gaaggttagag gcagccaaacg tgcacatcg cccgaagttt atcagcaatg
1561 gccccttcaa ggacactgtg accgtcaaga tcgcagtaga agatgtgtat gagcccccta
1621 tggcttggc cccaaagtac atccacgaa tccaaagaaaa tgcagctgct ggccaccgtgg
1681 ttggagagt gcatgccaaa gaccctgtat ctgccaacag cccgataagg tattccatcg
1741 atgctcacac tgacccgtac agattttca ctattaatcc agaggatggt ttattaaaa
1801 ctacaaaacc tctggataga gaggaaacag cctggctcaa catcactgtc ttgcagcc
1861 aaatccacaa tcggcatcag gaagccaaag tccctggc cattagggtc ttgtatgtca
1921 acgataatgc tcccaagttt gctggccctt atgaaggitt catctgtgag agtgcgtc
1981 ccaagccact tcccaaccag ccaattgtt caattgtgc agatgacaag gatgacacgg
2041 ccaatggacc aagatttac ttccgcctac cccctgaaat cattcacaat ccaaaattca
2101 cagtcagaga caaccggat aacacagcag gcgtgtacgc cccgcgtgg ggggtcagtc
2161 ggcagaagca ggacttgcac ttctgcctca tagtgcgtac cgtatggccgc atcccgccca
2221 tggatgtac caacaccctc accatcaaag tctgggggtg cgacgtgaac ggggcactgc
2281 tctctgcctca cgcagaggcc tacattctga acggccggct gggccatggc gccctgtatcg
2341 ccacccctgc ctgcacgtc attctctgg gttggccaaat cttatggaa cccccccttc
2401 ccagggaaga catgagattt tttatctgg gttccagct gatgtatcc ttctatgtt
2461 aagtaaacag aagattttgtt tttatgggg ttttataaa acttccttc ctctatgtgg
2521 tggatgtac gggatgggg gggatgggg tttatgggg tttatgggg tttatgggg
2581 gcaaaaagaaaa gaaccactca ttgttgcgt gggatgggg tttatgggg tttatgggg
2641 tttatgggg tttatgggg tttatgggg tttatgggg tttatgggg tttatgggg
2701 gatccatgtatcc gatccatgtatcc cccaaagac atcaaaacctg agtgcgt
2761 catgcctaga cttggctcc ggccagccgc caacagcgtg gatgtgcgt gatgtgcgt
acttcatcaat

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2821 cacgagaata caggagggcag acaatgaccc cacggctcct ccttatgact ccattcaaat
2881 ctacggttat gaaggcaggg gctcagtggc cggtccctg agtcgcctag agtgcggcac
2941 cacagattca gacttggact atgattatct acagaactgg ggacctcggt ttaagaaact
3001 agcagatttgc tatggttcca aagacacttt tgatgacgat tcttaacaat aacgatacaa
3061 atttggcctt aagaactgtg tctggcgltc tcaagaatct agaagatgtg taaaacaggta
3121 ttttttaaa tcaaggaaag gctcattaa aacaggcaaa gttttacaga gaggatacat
3181 ttaataaaac tgcgaggaca tcaaagtggt aaatactgtg aaataccctt tctcacaaaa
3241 aggccaaatat tgaagttgtt tatcaacttc gctagaaaaa aaaaacactt ggcatacaaa
3301 atatthaagt gaaggagaag tctaacfctg aactgacaat gaagggaaat tgtttatgtg
3361 ttatgaacat ccaagctttt ctctttttt aagttgtcaa agaagctcc acaaaattag
3421 aaaggacaac agttctgagc tgaatttcg ccttaaactc tggacactct atatgttagt
3481 cattttaaa ctgaaatat ataatttca gcacgttta acccatacaa tggatgtaca
3541 atacaatgtt caattatgtc tcttgagcat caatcttgc tttgtgtt actgtgttctt cttgtaaatc
3601 ttttgcttc tactttcatc ttaaactaat acgtgccaga tataactgtc ttgttcagt
3661 gagagacgcc ctattctat gtcatttta atgtatctat ttgtacaatt ttaaagttct
3721 tatttttagta tacatataaa tatcagtatt ctgacatgtt agaaaatgtt acggcatcac
3781 acttatattt tatgaacatt gtactgtgc tttaatatgtt gcttcaatat aagaagcaat
3841 ctgttggaaata aaaaaagatt tttttt

Figure 24. (Page 36 of 46)**NM_014935 Homo sapiens phosphoinositol 3-phosphate-binding protein-3 (PEPP)**

1 gctggatct gcagtaacca caacagcatc ctctccctgc gccagggacc tgccagccgg
61 agagatgact gattagatca gattagatcc ggagccccgc tctcagaag ggggccccag
121 gggggggga ggaggaccc agctggctg agctgggggg agggtgcct tggggctcgc
181 agagtttagag ctttccagcg cggggatcac acctcagaag ccgcacaat gaaagacgga
241 acacattct acaccagtg actggccagg tcccagagga aaacaaaaaa ttgacttga
301 aaatatcgac ctggacatg tccaataaaa caggtggaa acgccccgt accaccaaca
361 gtgacatacc caaccacaac atgggtccg aggtccctcc agagcggccc aegtccggg
421 caactcgcac agccgaaa gccatgcct tggcaagcg ctcacactcc atgaagcgga
481 accccaatgc acctgtcacc aaggcgggtt ggcttcaa acaggccagc tccggggta
541 aegagtggaa caagcgtgg ttgcgtctgg tggatgcgtg cctcttctac tataaagatg
601 agaaggaaga gagtatctcg ggcagcatcc ccctcctgag ctccggta gcccagtg
661 agccctcaga caacatcage cggaaacaca cgttaaggc tgagcatgcc ggggtccgca
721 cctacttctt cagtggcgag agcccgagg agcaagaggc ctggatccag gccatgggg
781 aggctgctcg agtacagat cttccagccccc agaagtca gcccagact gtgcggcaca
841 gccatgagaa gccagactcg gagaacgtcc cacccagcaa gcaccaccag cagccaccc
901 acaacagcct ccctaagcct gagccagagg ccaagactcg aggggagggt gatggccgag
961 gctgtgagaa ggcagagaga aggctgaga gcccagaagt caagaaagag cttccgtgt
1021 aagccaatgg cttcccatgt ggaccggagc cagcctcaga gcccggcagc cttaccc
1081 agggcccaag agtgcctagg ggtggggaaac agcctgcctt gccaatggc tggcagtacc
1141 actcccaag cggccaggg agcacagctt tccgtctca ggatggagag actgggggac
1201 accggggag ttcccacca cgcaccaacc ctgacaaaat tgcccagcgc aagagctca
1261 tgaaccagct tcagcagtgg gtgaatctgc gcccgggggt acccccgct gaagacctc
1321 ggagtcctc tagttctat cctgtgtctc gcagggtccc tgagttactat gcccctact
1381 cttcccgatgtatcgtact accegecagg agtgcggccg gagagcatct
1441 gttccatgcc ggcctatgtatcgtact accegecagg agtgcggccg gagagcatct
1501 cttcccgaa tgggggtggc cttgcctacc agtgcgaga gtggaggag ccccgagct
1561 acggccggca ggatgccacc gtgtggatcc caagccctc cggcagcca gtctattatg
1621 atgagctgga tggccctct agtccctgc gcccgtgc cctgcagccc cgctccact
1681 ctgtcccccg ctaccccagc cagggctctt acagccgtgc ccgcattac tcccctgtcc
1741 gtcaccccg tggccgtttt gaggggtgc cacctcgag tgaggacatc tatgtgacc
1801 ctgtgcctt tggatggggc cttccatca gtcacccctt ggtccctca tacccagaag
1861 tggccggca cttccatca acctacaatg taaacgagca agacacagat aagctgctgg
1921 gaaaattgtg tgagcagaac aagggtgtg gggagcagga cggctgggt cagcagctcc
1981 gagctgagaa ggagacccctg gaaatgtctt tgatggggac ccaccaggag ctggagatgt
2041 tggaaagcca gcccgcctac ccagaaaagc tgccacaaa aaaggattca ctgcagaacc
2101 agctcatcaa catccgcgtg gagctgtctc agggcaccac gcccgtaca aacaccc
2161 tagatgtatcgtact acctacaatg taaacgagca agacacagat aagctgctgg
2221 tcaatttggc caccctggatgatggatggcc accggcaat cccaaaggag atctggagga
2281 tccaggacgt gatggggggg ctgaggaaga acaacccctc cggggcagc gacaccgcca
2341 agcacagagg aggacttggc ccctcagcca cttccatca acaccccg gcccggcc
2401 tcagctctgc cttccatca accccctgtt gccccttcc actgggtgtc ggctctcagg
2461 ggtccccccac caagcctggc tccaaacggc ccaaggccaa ctatgacaa agcaagaaag
2521 accccacca gacattggcc ctggacaccc ccagagacat cagccgtgtg cccaccaggc
2581 aagaggttaga ggcagagagaag caggcagtc tcaacaaatg tggcgtgtg cccctcgga
2641 cccaaatcgcc cactgtatgtatgatggatggcc catcagcgtt ggttggaaagg aatggccagtg
2701 ggctcaccaa tggacttcc tccctggaaac gccccttcc gggccggcagg
2761 ggaaggtcaa gatggcgtg gaggagcaga ttgaccgaat gcccggcagc cagatggct

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2821 ccatgaaggga gaagcgggagg agcctgcagc tccccggccag cccggccccc gaccccgatc
2881 cccggccagc ctacaaagtgt gtgcgccgaccgcacat ccacgaggta gacatctcca
2941 acctggaggc agccctgcgg gcagaggagc ctggcgggca tgcctacgag acaccccgaa
3001 aggaaattgc cggcttcgc aaaaatggaggc tagagccca gcattatgac gtggacatca
3061 ataaggagct ctccactcca gacaaagtcc tcataccctga acggatcatt gacccctggagc
3121 ctgacactcc cctgagccctt gaggagttga aggagaagca gaagaagggtg gagaggatca
3181 agacactcat tgccaaatcc agtatgcaga acgtggtgc catccggcgg gggactctg
3241 tggacgtgcc ccaggactca gagagccagc tgcaggagca ggagaaggcg attgaaatct
3301 cctgegcctt ggcgaccgag gcctcccgca gggccgcattt gctgtctgt caatgtgcca
3361 ccccaagccc tcccacccctt cctgttcccc cggcccttcc agcaaaccctt ctgtgtctg
3421 aatccccacg gggcggccgac agcagctata ccatgcgggtt ctgagctctg actgcaagcc
3481 ctggctgagg ccaatgcgtgtt gaagctccac agagccacat tctgaagccg tcctctggccc
3541 acctgagggtc ctggctcccc accctggccc cctgccttcc cactccatg ggaatgcgc
3601 agggagccag gctggggcca tgggctgttcc cagaggacc gtggataacctt cagtgtccac
3661 acacccacca tggccagcccc tggagccatc actactcaca ccgtggctt gggccagggg
3721 ctgagatgac agtggggagc accatctca ttaatgttcca agtcacaggg agcctcagcc
3781 ttggccctggc tggggttgtt gttactccatg tggaaacattt cctgtatgggg gacatggcgt
3841 ggtggagaac acacctgtgg ctatcttatg tgaggacttag aggtgaagag gagatggaca
3901 ctgcctctgg agccagccctg acaccaaggaa cagacttgtt catcatccctt atcctctgtca
3961 gccccaccctt gtcgcctcag ctggaccccg ggctttgaca caaaaccctgtt gctttgttca
4021 tgggtgcctg ctggggctcg gtggagactg accacccctgc ttggccaaa gacaagggtga
4081 tgagagatgg ggagaggcca ttggctccca gagggaacag tgctggctgt ggcttagagaa
4141 cagcagggtctt gtcgtgtc tgagggcagg ttgggaaggg tagcagagag agagagac
4201 aaagagagag agagagagag agagagagag agagagatcc tcagagtgg
4261 aggagggggaa agcagcagga cacattggca agtcaagcag gaaggaggaa gatggaaagg
4321 ggatatcaga ttggttcccc ccgggtggagc ctttaggttag tgccctgtc agtgcac
4381 tgtctccctt gtcctccca cctcatccctt aggaggaccc accagtggag cacatgc
4441 ctcatggag atgctttgtt tggggatctg ggtgaagggg gtttgatgtc gactgcctgg
4501 gagatggctt ttagtagtgc tgcccttggt gtctgcctcg ccattctggg gtaaggggca
4561 gagagaaggaa ctgttctttagt gtgggtgtt gtcagccctt gggccattacc tacccagg
4621 catgatattt ctggccctgtt tccccctggaa atgtgcagttt ggcctatccca ggcattcc
4681 tgaggagggggg ggatggggcc ttaatctggg aggccatcc cccatccca ggcattcc
4741 acggggactg gtcgtgttca ggcgttca tgatccatcc gccccgggag ggccatgggg
4801 aagacagaga aaagcaaaca cattccctt cagctccacc cacctggaga cgaatgttag
4861 cagagaggag gaaggaggaa aactgaaaac accgtggccc ctggcccttc tctctgttag
4921 agttggccgtt cagaggcttc agcctgactt ccagccgttcc caagaacacc tactaattcc
4981 ttcctccatcc ttcatggctt ggcacatccat gcaagtaaag atgacaattt
5041 actcaac

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M61906 Human PI3-kinase, p85 subunit

1 tacaaccagg ctaaactgtt gcatggtagc agatttgc aaatgagttc tgagggtac
61 cagtagcagg cgctgtatga ttataaaaag gaaagagaag aagafattga ctgcacttg
121 ggtgacatat tgactgtgaa taaagggtcc tttagtagctc ttggatttc tgatggacag
181 gaagccaggc ctgaagaaaat tggctggta aatggctata atgaaaccac aggggaaagg
241 ggggactttc cgggaaactt cgtagaatat attggaagga aaaaaatctc gcctccca
301 ccaaagcccc ggcccacccgc gcctcttcc ttgcaccagg gccttcgaa aactgaagca
361 gatgttgaac aacaagctt gactctcccg gatcttcgag agcaggttc ccctctgac
421 attgccccgc ctcttctt caagctcggtt gaagccattt aaaagaaaagg tctgaaatgt
481 tcaactctat acagaacaca gagctccagc aacctggcag aattacgaca gcctcttgc
541 tgtgatacac cctccgtgaa ttggaaatg atcgatgtc acgtttggc tgacgcttc
601 aaacgctatc tcctggactt accaaatctt gtcattccag cagccgttta cagtggaaatg
661 atttcttag ctccagaatg acaaagctcc gaagaatata ttcaagttt gaagaagctt
721 attaggtcgc cttagcatacc tcatacgatg tggcttacgc ttcaagttt gttaaaacat
781 ttctcaagc tcctctaaac ctccagcaaa aatctgttga atgcaagagt actctctgaa
841 atttcagcc ctatgctttt cagattctca gcagccagct ctgataatac tgaaaaccc
901 ataaaagttt tagaaatttt aatctcaact gaatggaaatg aacgcacagcc tgccaccaggca
961 ctggctcttta aaccaccaaa acctactact gttagccaaca acggatggaa taacaatatg
1021 tccttacaaa atgctgaatg gtactgggg gatatctga ggggaaatg gaatggaaa
1081 ctccgagata cagcagacgg gaccctttt gtagcggatg cgtctactaa aatctcatgg
1141 gaitatactc ttacactaaag gaaagggggaa aataacaaaat taatcaaaaat atttcatcg
1201 gatggggaaat atggcttctc tgaccattt accttcgatg ctgtgggttga attaataaac
1261 cactaccggg atgaatctct agtcctgtt aatccaaat tggatgttga attacattt
1321 ccagtatcca aataccaaaca ggatcaagtt gtcaaaaggaatg ataataatttga agtcgttaggg
1381 aaaaaattac atgaatataa cactcgtt caagaaaaaa gtcgagaata tgatgatgat
1441 tatggaaat atacccgcac atcccgaggaa atccaaatga aaaggacagc tattggaa
1501 ttaatgaaa ccataaaaaat attgaaatg cagtgcggc cccaaagagcg gtacagcaaa
1561 gaatacatag aaaagtttac acgtgaaggc aatggaaatg aaatacaaaag gattatgc
1621 aattatgata agttgaagtc tcgaatcagt gaaatttattt acagttggaa aagattggaa
1681 gaagacttga agaaggcaggc agctggatg cggaaaatttgc acaaaccgtt gaacaggatt
1741 aaaccagacc ttatccagct gggaaagacg agagaccaat acttgcatttgc ttgtactca
1801 aaagggttcc ggccaaagaa gttgaacggc tgggtggcata atggaaaacac tgaagacc
1861 tatttcacttgg tggaaagatgatg tgaagattttt cccatcatg atgagaagac atggatgtt
1921 ggaagcagca accggaaacaa agctggaaac ctgttgcggag ggaagcggaga tggacttt
1981 ctggccggg agagcagttt acagggttgc tatgcctgtt ctgtatgtt ggcggcggaa
2041 gtaaaaggcatt ttgttgcataaa caaaacagca actggctatg gcttgcggc gcccataaac
2101 ttgtacagct ctgttgcataaa cattaccaac acacccttgc ttttgcggc
2161 aacgactccc tcaatgtcactt actggcttcc cctgtatgtt cacaggcaggc ggcgttgc
2221 gcttactttt ttgttgcataaa ctttttttttgc ttttgcggc
2281 gcttacttgc agtgcgttgc ttgttgcggc ttttgcggc
2341 gggacttagag ctgttgcataaa ctttttttgc ttttgcggc
2401 ttgttgcataaa ctttttttttgc ttttgcggc
2461 ttaatttaaa ggcacacca catacaacac aaaggaaaaaa agaaatgc
2521 ttgttgcataaa ctttttttttgc ttttgcggc
2581 gcttacttgc ttttgcggc
2641 agtgcgttgc ttttgcggc
2701 gcttacttgc ttttgcggc
2761 ctcaacaggc acgcttttttttgc ttttgcggc

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2821 agaaagtgc agaaagtgtt taacttgtca aaaaacaaaa acccagcaac agaaaaatgg
2881 agttggaaa acaggactta aaatgacatt cagtataaa aatatgtaca taatatttga
2941 tgactaacta tcaaatacatatggatggatgttatcaataccaaa tagttctgtttttgc
3001 tgaaggctaa attcacagcg ctatgcaatt cttaaatttc attaagtgttatttcagtt
3061 taaaatgtac ctccagaata agctccccca ccccagtttt tggtgcgttga aaatattgtt
3121 gtccggatt ttgttaata ttcatttttg ttatcccttt taaaaataaa atgtacagga
3181 tgccagtaaa aaaaaaaatg gttcagaat taaaactatg aaatatttta cagttttct
3241 tgtacagagt acttgctgtt agcccaaggtaaaaaagttc ataacagatt tttttggac
3301 tgttttgttg ggcagtgcct gataagcttc aaagctgctt tattcaataaa aaaaaaaacc
3361 cgaattcact gg .

Figure 24. (Page 40 of 46)**J05582 Human mucin 1**

1 ccgttccacc tcgtcaagcag ccagcgctg cctgaatctg ttctggcccc tccccaccca
61 ttccaccacc accatgacac cgggcaccca gtcctttc ttccctgtgc tgctcctcac
121 agtgcttaca gttgttacag gttctggta tgcaagctt accccagggtg gagaaaaggaa
181 gacttcggct acccagagaa gttcagtgcc cagctctact gagaagaatg ctgtgagtt
241 gaccagcagc gtactctca gccacagccc cgggtttaggc ttctccacca ctcaggagaca
301 ggatgtcaact ctggcccccgg ccacggaaacc agcttcagggt tcagctgcc cctggggaca
361 ggatgtcacc tgggtcccgag tcaccaggcc agccctgggc tccaccaccc cggcagccca
421 cgatgtcacc tcagccccgg acaacaagcc agccccgggc tccaccgccc ccccaagccca
481 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
541 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
601 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
661 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
721 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
781 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
841 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
901 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
961 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1021 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
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1141 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1201 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1261 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1321 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1381 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1441 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1501 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1561 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1621 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
1681 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
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1921 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
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2041 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
2101 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
2161 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
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2641 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
2701 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca
2761 cggtgtcacc tggccccggg acaccaggcc ggccccgggc tccaccgccc ccccaagccca

Figure 24. (Page 41 of 46)

2821 cgggtgcacc tcggcccccgg acaccaggcc ggccccggc tccaccgccc ecccagccca
2881 tgggtgcacc tcggcccccgg acaaacaggcc cgccttggc tccaccgccc ctccagtc
2941 caatgtcacc tcggcctcgag gctctgcata aggtcgact tctactctgg tgcaacaacgg
3001 cacctctgcc agggtacca caaccccagc cagcaagagc actccattt caattccag
3061 ccaccactt gatacttcta ccacccttc cagccatagc accaagactg atgccagtag
3121 cactcaccat agtcggta ctccttcac ctcttcaat cacagcactt ctccccagtt
3181 gtctactggg gtcttttct ttccctgtc ttccatcatt tcaaacctcc agtttaattc
3241 ctctctggaa gatcccgaea ccgactacta ccaagagctg cagagagaca ttctgaaat
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3421 cgtggagaca cagttaatc agtataaaaac ggaagcagcc tctcgatata acctgacgat
3481 ctcagacgtc agcgtgagtg atgtgcatt tcccttc tcccgactg gggctgggt
3541 gccaggctgg ggcatcgcc tgcgtgtgtt ctgggtgcgc tgccatttg
3601 ctatctcatt gccttggctg tctgtcagtg ccgcgaaag aactacggc agctggacat
3661 cttccagcc cgggataacctt accatccat gaggcgatc cccacccatc acacccatgg
3721 gcgcgtatgtg ccccttagca gtaccgtatcg tagcccttat gagaagggtt ctgcaggtaa
3781 cggtggcagc agccctctt acacaaaccc agcgtggca gccgcttctg ccaacttga
3841 gggcactgtcg ccgcgtgatct ggttggccag ccagtgccat tccactccac tcaggttt
3901 caggccagag cccctgcacc ctgtttggc tggtgagctg ggagttcagg tgggctgtc
3961 acagccctt tcagagggcc caccaattt tcggacactt ctcaatgtgtt ggaagctcat
4021 gtggggccctt gaggtctatg cttgggaagt gtttgtgggg ctcccaggag gactggccca
4081 gagagccctg agatagcggg gatccctgaac tggactgaat aaaacgtgtt ctcccaactg

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M29366 Human Epidermal Growth Factor Receptor (ErbB3)

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2821 gggcagagc cctatgcagg gctacgattt gctgaagtac cagacctgct agagaagggg
2881 gagcggttgg cacagccccca gatctgcaca attgatgtct acatggtgat ggtcaagtgt
2941 tggatgattt atgagaacat tcgccccacc tttaaagaac tagccaatga gttcaccagg
3001 atggcccgag acccaccacg gatatctggtc ataaaagagag agagtgggcc tggaaatagcc
3061 cctggccag agccccatgg tctgacaaac aagaagctag aggaagtaga gctggagcca
3121 gaactagacc tagacctaga ctggaaagca gaggaggaca acctggcaac caccacactg
3181 ggctccgccc tcagectacc agtttggaca cttaatcgcc cacgtggag ccagagcctt
3241 ttaagtccat catctggata catgcccattt aaccaggta atcttgggaa gtcttggcag
3301 gagtctgcag ttctgggag cagtgaaacgg tgcccccgtc cagtcctctt acacccaatg
3361 ccacggggat gcctggcatc agagtcatac gaggggcatg taacaggctc tgaggctgag
3421 ctccaggaga aagtgtcaat gtgttagaagc cggagcagga gccggagccc acggccacgc
3481 ggagatagcg cttaccatttc ccagcgccac agtctgttgc cttctgttac cccactctcc
3541 ccacccgggt tagaggaaga ggatgtcaac ggttatgtca tgccagatac acacctcaa
3601 ggtactccct cttccggga aggccaccctt tttcagtgg gtcttagttc tgtctgggt
3661 actgaagaag aagatgaaga tgaggagttt gaatacatga accggaggag aaggcacagt
3721 ccacctcatc ccccttagggc aagtccctt gaggagctgg gttatgagta catggatgt
3781 gggtcagacc tcagtgccctc tctggcagc acacagagtt gcccactcca ccctgttaccc
3841 atcatgccccttc ctgcaggccac aactccatgtt gaagactatg aatataatgaa tcggcaacga
3901 gatggagggtg gtccctgggg tgattatgca gccatggggg cctgcccagc atctgagcaa
3961 gggatgtaaag agatgagagc ttttcagggg cctggacatc aggccccca tgtccattat
4021 gccccctaa aaactctacg tagcttagag gctacagact ctgccttga taaccctgtat
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4501 actgtcaaga agaggaaagg gaggaaacctt agcagaggaa agtgtaattt tggttatgaa
4561 ctcttaaccc cctagaaaga cagaagctttaa aatctgttga agaaagaggt taggagtaga
4621 tattgattac tatcataattt cagcacttaa ctatgagcca ggcatac taaacttcac
4681 ctacatttac tcaacttagtc ctttatcatc cttaaaacaa ttctgtgaca tacatattat
4741 ctcatttac acaaaggaa gtcggccatg gtggctcatg cctgttaatctt cagcacttt
4801 ggaggctgag gcagaaggat tacctgaggc aaggagttt agaccagctt agccaacata
4861 gtaagacccc catctcttt

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Homo sapiens gene for hepatitis C-associated microtubular aggregate protein p44

D28908 Exon 1 and 2

1 gaattctgaa tataggacac gaatttatga tccttagcaa tgtgaagttt gagaagggtt
61 ttatttgta aattgacaca gggtgttta tacttataa atgaagtc ctcatttcc
121 tgtggcaga agagaggggg caagcagaaa agcagaggaa caaatttggg ggctaaaata
181 acatttaca taaggaacta tactacagta gaattaattt atagcaggaa ttaagagatg
241 taaatgaatt tgagatacat attctagagg tagaatgtgc aatactttt gtatgtccat
301 atacagaaaat tggtgcatt ttcccttaat aaaaagattt tttaaaagtc agtgagctgt
361 tatgtttct tccctctgac ttcaatttcc ttgatttttc aatttttttta atataaattt
421 actgtctaaa agtggatca getttagtgc ctttgttag agaagtggc atgctgtcaa
481 gtgggtggg cacactgagt ttcaagttcc ttctctgag tctttgaagc ttcaaggctg
541 ctgaataattt tccttctccc attttgtgcc tgccctagcta tccagacaga gcagctaccc
601 tcagctctg ctgatactac agacagtaca acaggtaat gtcttctgc ttttcattt
661 tcctagctg cattagtctc tcctctgtc tctcaggta cagtgccat tgcaatctca
721 gtttttgtt taattaaaa aacaataattt tatagtaaaa aatttagctaa tgattttttt
781 gcttctgtt catcctttt tttgtcattt ttgttattt gttaggtata taagaggcat
841 aaatgcaaat ttataacta catattatct gtttttaat attaatggaa aataatataat
901 gattgccac tagatcaaga agtatggcg tgacaactcg ttgcacatgg ttgcacgaaa
961 agatctgc aaatcattttt ggaggggaagc ggcttagct tctctataag ggtatgtcc
1021 atggattccg taatggagt ttgcgtgaca gatgttgtaa tcaaggccct actctaacag
1081 tgattttag tgaagatcat attatggag catatgcaga agagagttac caggaaggaa
1141 agtatgttc catcatcctt ttgcacttc aagataactaa aatttcagaa tggaaactag
1201 gactatgtac accagaaaca ctgttttgtt gtgtatgtac aaaatataac tccccaaacta
1261 atttccagat agatggaaaga aatagaaaaag tgattatggaa cttaaagaca atggaaaatc
1321 ttggacttgc tcaaaatgt actatctta ttcaaggat tgaagttttt cgatgcgaag
1381 gtaggtttaa ttgataatc ctgttagagag ttctcccttg catgtttggt aggtttgaac
1441 caatcatct cttaaggaa aatgaactt ttcaacttgc aataatttgg atgattcaga
1501 ctgaaacctg gatacagatt ttgtgctaag agacaaccat ggtcaataaa atgtatattt
1561 atgataagaa cccttaacgt aagatttac ctcttagcac attttaagta c

D28909 **Exon 3**

1 gaattcactg atattcattc attcattcg ccaattattc gacaacttct aatctacatt
61 atctttgtat tatttccccca gattcactgg atgaaaagaaa gataaaaggg gtcatttgagt
121 aagtcaatgt tttaagatt ctattactct ctcca

Figure 24. (Page 45 of 46)**D28910 Exon 4**

1 ttgcgacct aacctcagtc aattgtaaa aacggcatg tctaaacagg ctcaggaaga
61 gcttactg tccttgaga acitatac catatggatc cctggtaaa caaatacgaa
121 ttctccctt gggccaatt ggagctcca agtccagtt ttcaactca gtgaggctg
181 tttccaagg gcatgtaacg cataggctt tggggcac taatacaact gggatatctg
241 agaaggtaa cacatttgag gccacctagc ctggctct ctgtcaaat caattatatt
301 tcaaaagctt tt

D28911 Exon 5

1 ggccacccat ccttgcctc tctgtcaaa tcaattat tcaaaaagcc ttgcagat
61 caactttatt acatatac ttcatctcaa ttataataaa aaaatgaatc ttaaaattg
121 ctttctccc ctctacagta taggacatac tctatttagag acggaaaga tggcaaatac
181 ctgccgtta ttctgtgtca ctcactgggg ctgagtgaga aagaaggcg cctgtgcagg
241 gatgacat tctatatctt gaacggtaac attcgtgata gataccaggt aatatttgc
301 taatgagaaa ttataactga tttaaaaat gcttattttt gtacaatgt atcagcgttt
361 atcttcattttaa attatacttg ctcaagatcc ttgtctt tttagattttt ttttcaaaa
421 agaataaaaaa catctcgagg gctttc

D28912 Exon 6

1 ttgtgcctat aaatatttg tgaattaata tcttgctta tgcgtacattt acagtttat
61 cccatggaaat caatcaaattt aaatcatcat gactacattt attccccatc gctgaaggac
121 agaatttcattt gtgtggcatt tgiatttgat gccagctcta tcaataactt ccctctcag
181 atgatagttaa agatcaaagg aattcaaagg gagttggtaa acgttgtga gtcttattcc
241 actttgctaa gggtaatacc actaagggtt attgactaga ctgtattttt gaatgtttt
301 tggacaggat aaagaactta agtcatttca tatttcaatc t

D28913 Exon 7

1 gatcttcca aatctgaaat tggccatag gttgcctattt acataatttga tagttaaata
61 acttgaaaat actgtgtc tctaaaatga tttaaaaat tctgtttggc ataggtgtgg
121 tacatgtggc ttgtctactt catgtggata gcatggattt gattacaaaaa ggtgacccca
181 tagaaataga gagatgttag cctgtggatgtt ccaaggtaat gaatgtgcc ctgcgtaaac
241 acattttctg gggtagtta ctacaatcac atactgtgtt gtataaaa

Figure 24. (Page 46 of 46)**D28914 Exon 8**

1 ttttttcca atggaaatta ttgcaagttc ctacatcttg atattgcitt cataatttat
61 actaacataa aataatattt ttcaactgttt tgcaatgtct ttttaatttc tgtattgcag
121 ctagaggaag tccaaagaaa acttggattt gctcttcgt acatctcggt ggtagcaat
181 tattccctctg agtggagct ggaccctgt aaggatgttc taattcttc tgctctgaga
241 cgaatgcstat gggctgcaga tgacttcta gaggatttgc ctttgagca aataggtaga
301 tggtttggtg gtgttggaaagc ttggaaagcgg tcaggtagtt ggctacttgc tgctggatc
361 tattaaatac tg

D28915 Exon 9

1 cctctggtttgc ctttcctga gataatccac taagaatattt ttgtgtttctt ttctcaggg
61 aatctaaggg agggaaattt caactgtgca caaggaaaaaa aatagatgt tgaaaggttc
121 acgttaaattt cctcacatca cagaagatta aaattcagaa aggagaaaaac acagacccaa
181 gagaagtatc taagacaaa gggatgtttt ttattatgt ctaggatgaa gaaatgcata
241 gaacattgtt gtaattgttta ataacttagaa ataacatgtt ttagtcataa ttgtgaaaaa
301 taataataat tttcttgaa ttatgtttt gtatctgtga aaaaataaat ttcttataaaa
361 actcggtct aacttgagag tttgtgtgtat ttggaaaaaa ttatgttttgc ttagcatctt
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481 ttt

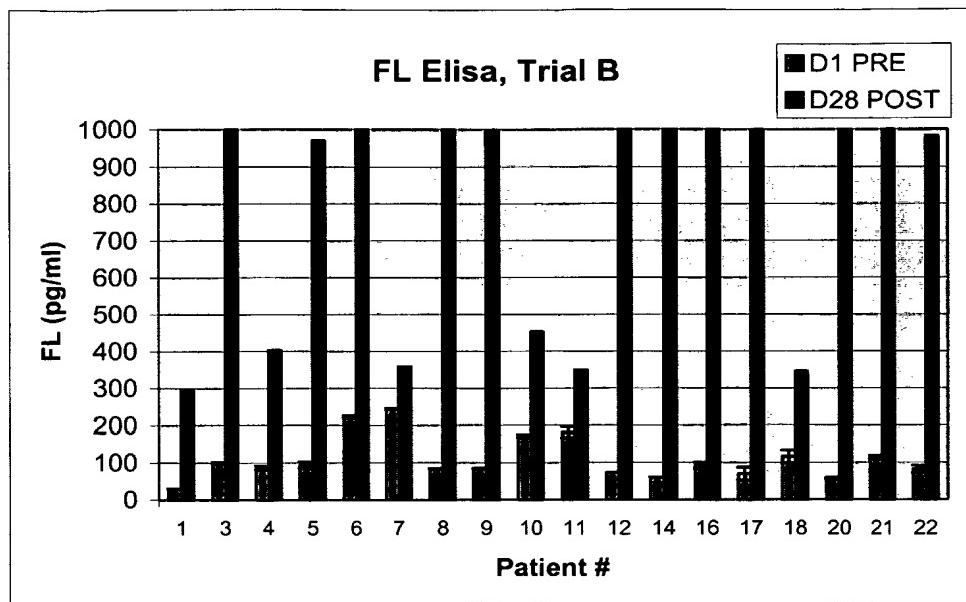
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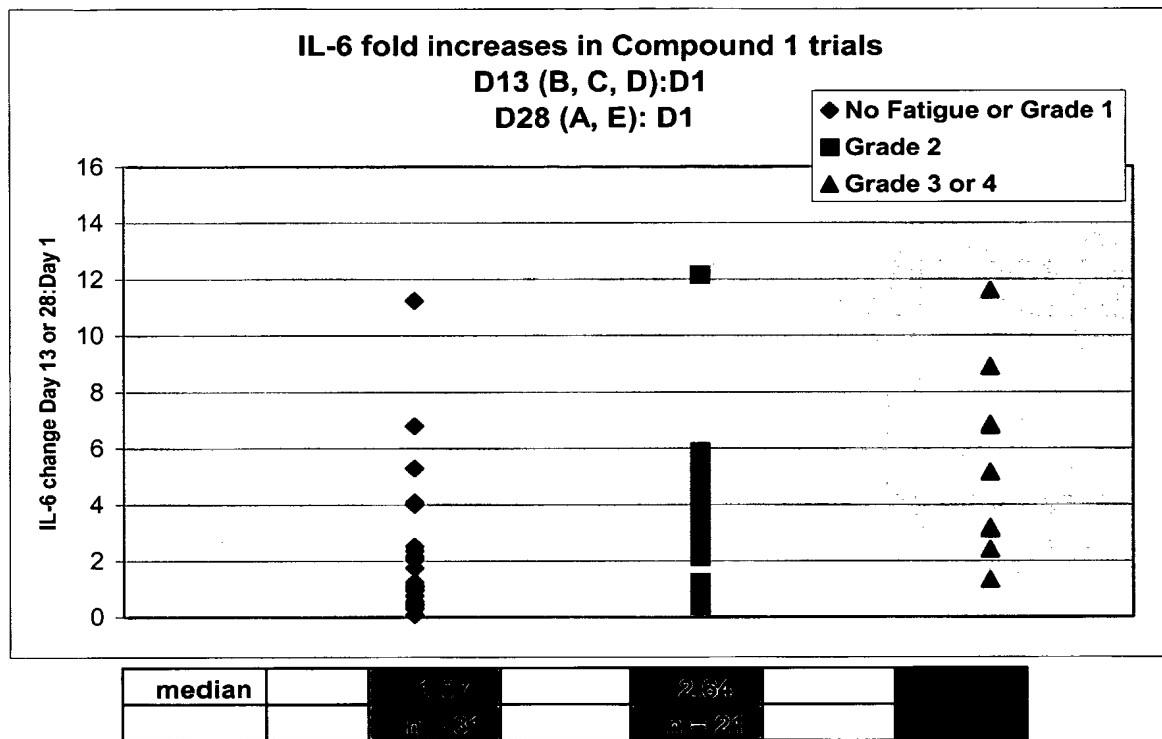
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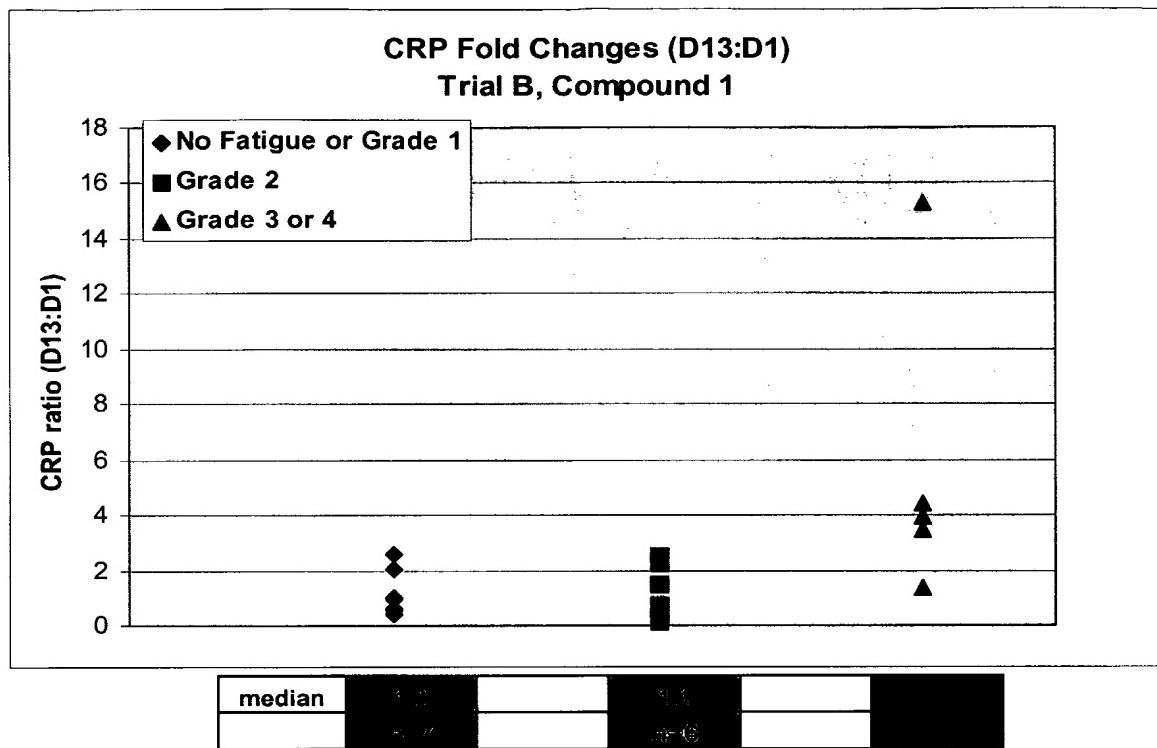
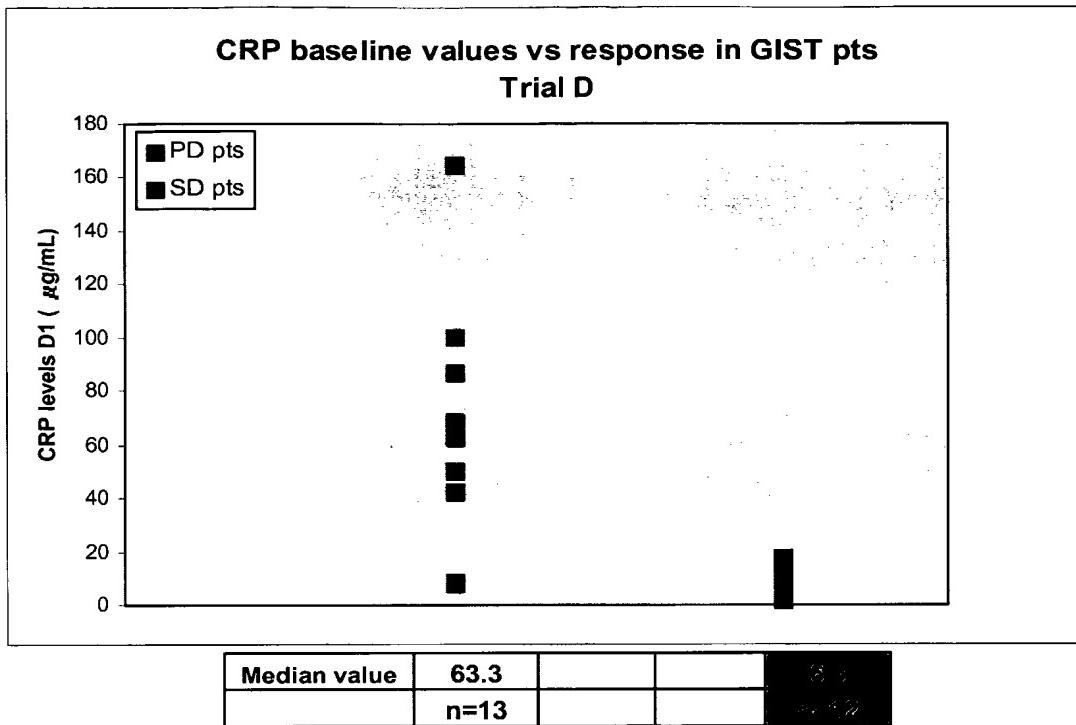
Figure 27.

Figure 28.

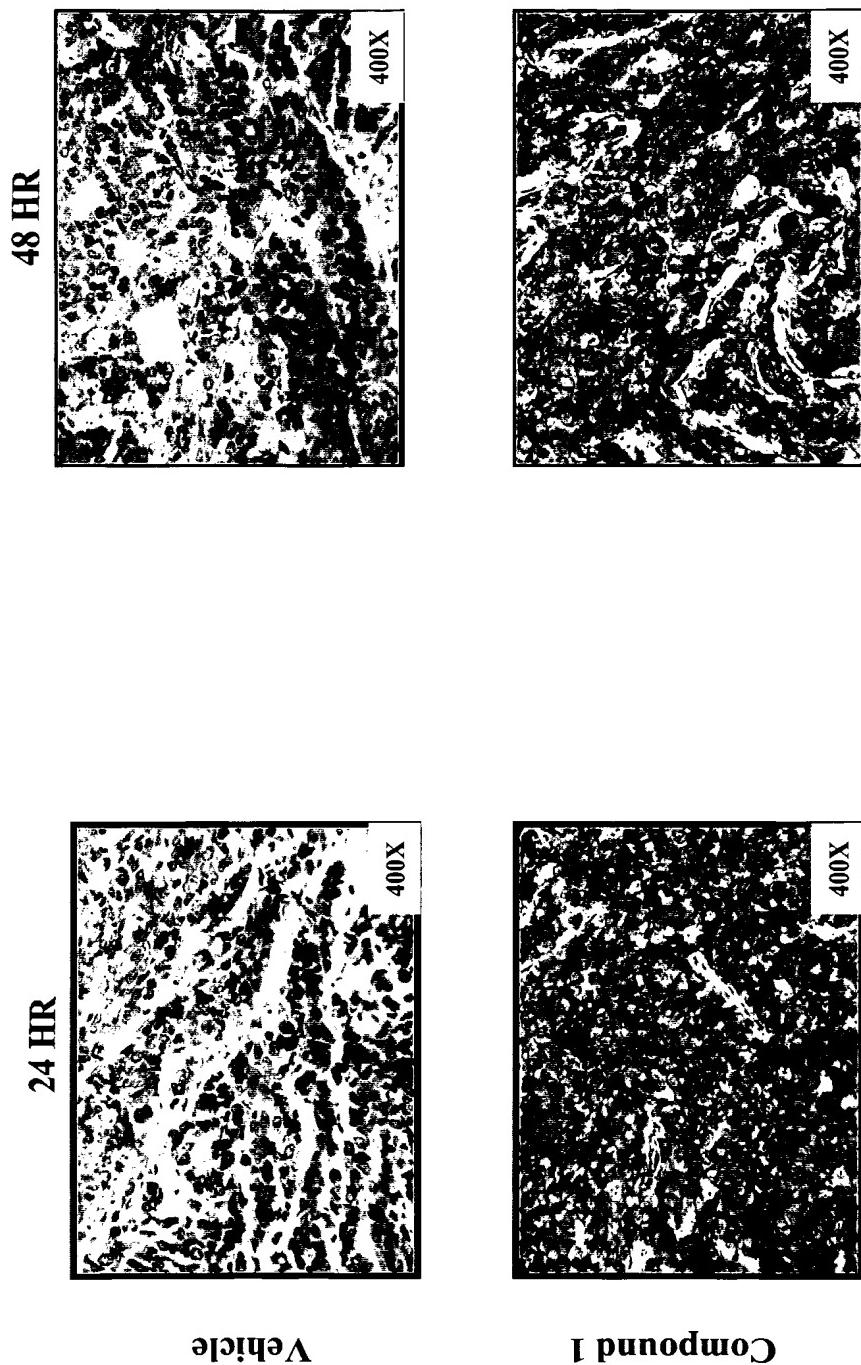


Figure 29.

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SEQUENCE LISTING

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<151> 2003-02-24

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<160> 185

<170> PatentIn Ver. 2.1

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<212> DNA
<213> Artificial Sequence

<220>
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<210> 3
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 31
tcagccagct taaacccata caa 23

<210> 32
<211> 29
<212> DNA
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: Primer

<400> 32
tggcacgtat tagtttaaga tgaaagtag 29

<210> 33
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 33
cttgttactg ctgattct 18

<210> 34
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 34
ttcagaggcc ccaccaatt 19

<210> 35
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 35
cccacatgag cttccacaca 20

<210> 36
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 36
tctcgacac ttctc 15

<210> 37
<211> 22

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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 37
tgaggcaggg acaagtcttt ct

22

<210> 38
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 38
accctgactg aaggctcatg a

21

<210> 39
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 39
ctctttgaga ccccaagtgc

19

<210> 40
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 40
tctaccgtcc ttgtcataac ttttgt

26

<210> 41
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 41
atgatgatgg gcccctgtt

19

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<210> 42
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 42
cctttgccca agttg 15

<210> 43
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 43
tggacgttt gtgatcgaag ag 22

<210> 44
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 44
aagtcaaggc ttctgtcttt tcttct 26

<210> 45
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 45
cttgagaatc ctttccaacc 20

<210> 46
<211> 10
<212> PRT
<213> Homo sapiens

<400> 46
Asp Ile Tyr Ser Ser Phe Gly Phe Pro Arg
1 5 10

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<210> 47
<211> 11
<212> PRT
<213> Homo sapiens

<400> 47
Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg
1 5 10

<210> 48
<211> 114
<212> PRT
<213> Homo sapiens

<400> 48
Met Ser Leu Leu Ser Ser Arg Ala Ala Arg Val Pro Gly Pro Ser Ser
1 5 10 15

Ser Leu Cys Ala Leu Leu Val Leu Leu Leu Leu Thr Gln Pro Gly
20 25 30

Pro Ile Ala Ser Ala Gly Pro Ala Ala Ala Val Leu Arg Glu Leu Arg
35 40 45

Cys Val Cys Leu Gln Thr Thr Gln Gly Val His Pro Lys Met Ile Ser
50 55 60

Asn Leu Gln Val Phe Ala Ile Gly Pro Gln Cys Ser Lys Val Glu Val
65 70 75 80

Val Ala Ser Leu Lys Asn Gly Lys Glu Ile Cys Leu Asp Pro Glu Ala
85 90 95

Pro Phe Leu Lys Lys Val Ile Gln Lys Ile Leu Asp Gly Gly Asn Lys
100 105 110

Glu Asn

<210> 49
<211> 120
<212> PRT
<213> Homo sapiens

<400> 49
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Arg Val Thr Lys Asp Ala Glu Thr Glu Phe Met
20 25 30

Met Ser Lys Leu Pro Leu Glu Asn Pro Val Leu Leu Asp Arg Phe His
35 40 45

Ala Thr Ser Ala Asp Cys Cys Ile Ser Tyr Thr Pro Arg Ser Ile Pro
50 55 60

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Cys Ser Leu Leu Glu Ser Tyr Phe Glu Thr Asn Ser Glu Cys Ser Lys
65 70 75 80

Pro Gly Val Ile Phe Leu Thr Lys Lys Gly Arg Arg Phe Cys Ala Asn
85 90 95

Pro Ser Asp Lys Gln Val Gln Val Cys Met Arg Met Leu Lys Leu Asp
100 105 110

Thr Arg Ile Lys Thr Arg Lys Asn
115 120

<210> 50

<211> 902

<212> PRT

<213> Homo sapiens

<400> 50

Met Ser Glu Phe Arg Ile His His Asp Val Asn Glu Leu Leu Ser Leu
1 5 10 15

Leu Arg Val His Gly Gly Asp Gly Ala Glu Val Tyr Ile Asp Leu Leu
20 25 30

Gln Lys Asn Arg Thr Pro Tyr Val Thr Thr Thr Val Ser Ala His Ser
35 40 45

Ala Lys Val Lys Ile Ala Glu Phe Ser Arg Thr Pro Glu Asp Phe Leu
50 55 60

Lys Lys Tyr Asp Glu Leu Lys Ser Lys Asn Thr Arg Asn Leu Asp Pro
65 70 75 80

Leu Val Tyr Leu Leu Ser Lys Leu Thr Glu Asp Lys Glu Thr Leu Gln
85 90 95

Tyr Leu Gln Gln Asn Ala Lys Glu Arg Ala Glu Leu Ala Ala Ala Ala
100 105 110

Val Gly Ser Ser Thr Thr Ser Ile Asn Val Pro Ala Ala Ala Ser Lys
115 120 125

Ile Ser Met Gln Glu Leu Glu Glu Leu Arg Lys Gln Leu Gly Ser Val
130 135 140

Ala Thr Gly Ser Thr Leu Gln Gln Ser Leu Glu Leu Lys Arg Lys Met
145 150 155 160

Leu Arg Asp Lys Gln Asn Lys Lys Asn Ser Gly Gln His Leu Pro Ile
165 170 175

Phe Pro Ala Trp Val Tyr Glu Arg Pro Ala Leu Ile Gly Asp Phe Leu
180 185 190

Ile Gly Ala Gly Ile Ser Thr Asp Thr Ala Leu Pro Ile Gly Thr Leu
195 200 205

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Pro Leu Ala Ser Gln Glu Ser Ala Val Val Glu Asp Leu Leu Tyr Val
210 215 220

Leu Val Gly Val Asp Gly Arg Tyr Val Ser Ala Gln Pro Leu Ala Gly
225 230 235 240

Arg Gln Ser Arg Thr Phe Leu Val Asp Pro Asn Leu Asp Leu Ser Ile
245 250 255

Arg Glu Leu Val His Arg Ile Leu Pro Val Ala Ala Ser Tyr Ser Ala
260 265 270

Val Thr Arg Phe Ile Glu Glu Lys Ser Ser Phe Glu Tyr Gly Gln Val
275 280 285

Asn His Ala Leu Ala Ala Ala Met Arg Thr Leu Val Lys Glu His Leu
290 295 300

Ile Leu Val Ser Gln Leu Glu Gln Leu His Arg Gln Gly Leu Leu Ser
305 310 315 320

Leu Gln Lys Leu Trp Phe Tyr Ile Gln Pro Ala Met Arg Thr Met Asp
325 330 335

Ile Leu Ala Ser Leu Ala Thr Ser Val Asp Lys Gly Glu Cys Leu Gly
340 345 350

Gly Ser Thr Leu Ser Leu Leu His Asp Arg Ser Phe Ser Tyr Thr Gly
355 360 365

Asp Ser Gln Ala Gln Glu Leu Cys Leu Tyr Leu Thr Lys Ala Ala Ser
370 375 380

Ala Pro Tyr Phe Glu Val Leu Glu Lys Trp Ile Tyr Arg Gly Ile Ile
385 390 395 400

His Asp Pro Tyr Ser Glu Phe Met Val Glu Glu His Glu Leu Arg Lys
405 410 415

Glu Arg Ile Gln Glu Asp Tyr Asn Asp Lys Tyr Trp Asp Gln Arg Tyr
420 425 430

Thr Ile Val Gln Gln Gln Ile Pro Ser Phe Leu Gln Lys Met Ala Asp
435 440 445

Lys Ile Leu Ser Thr Gly Lys Tyr Leu Asn Val Val Arg Glu Cys Gly
450 455 460

His Asp Val Thr Cys Pro Val Ala Lys Glu Ile Ile Tyr Thr Leu Lys
465 470 475 480

Glu Arg Ala Tyr Val Glu Gln Ile Glu Lys Ala Phe Asn Tyr Ala Ser
485 490 495

Lys Val Leu Leu Asp Phe Leu Met Glu Glu Lys Glu Leu Val Ala His
500 505 510

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Leu Arg Ser Ile Lys Arg Tyr Phe Leu Met Asp Gln Gly Asp Phe Phe
515 520 525

Val His Phe Met Asp Leu Ala Glu Glu Glu Leu Arg Lys Pro Val Glu
530 535 540

Asp Ile Thr Pro Pro Arg Leu Glu Ala Leu Leu Glu Leu Ala Leu Arg
545 550 555 560

Met Ser Thr Ala Asn Thr Asp Pro Phe Lys Asp Asp Leu Lys Ile Asp
565 570 575

Leu Met Pro His Asp Leu Ile Thr Gln Leu Leu Arg Val Leu Ala Ile
580 585 590

Glu Thr Lys Gln Glu Lys Ala Met Ala His Ala Asp Pro Thr Glu Leu
595 600 605

Ala Leu Ser Gly Leu Glu Ala Phe Ser Phe Asp Tyr Ile Val Lys Trp
610 615 620

Pro Leu Ser Leu Ile Ile Asn Arg Lys Ala Leu Thr Arg Tyr Gln Met
625 630 635 640

Leu Phe Arg His Met Phe Tyr Cys Lys His Val Glu Arg Gln Leu Cys
645 650 655

Ser Val Trp Ile Ser Asn Lys Thr Ala Lys Gln His Ser Leu His Ser
660 665 670

Ala Gln Trp Phe Ala Gly Ala Phe Thr Leu Arg Gln Arg Met Leu Asn
675 680 685

Phe Val Gln Asn Ile Gln Tyr Tyr Met Met Phe Glu Val Met Glu Pro
690 695 700

Thr Trp His Ile Leu Glu Lys Asn Leu Lys Ser Ala Ser Asn Ile Asp
705 710 715 720

Asp Val Leu Gly His His Thr Gly Phe Leu Asp Thr Cys Leu Lys Asp
725 730 735

Cys Met Leu Thr Asn Pro Glu Leu Leu Lys Val Phe Ser Lys Leu Met
740 745 750

Ser Val Cys Val Met Phe Thr Asn Cys Met Gln Lys Phe Thr Gln Ser
755 760 765

Met Lys Leu Asp Gly Glu Leu Gly Gly Gln Thr Leu Glu His Ser Thr
770 775 780

Val Leu Gly Leu Pro Ala Gly Ala Glu Glu Arg Ala Arg Lys Glu Leu
785 790 795 800

Ala Arg Lys His Leu Ala Glu His Ala Asp Thr Val Gln Leu Val Ser
805 810 815

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Gly Phe Glu Ala Thr Ile Asn Lys Phe Asp Lys Asn Phe Ser Ala His
 820 825 830

Leu Leu Asp Leu Leu Ala Arg Leu Ser Ile Tyr Ser Thr Ser Asp Cys
 835 840 845

Glu His Gly Met Ala Ser Val Ile Ser Arg Leu Asp Phe Asn Gly Phe
 850 855 860

Tyr Thr Glu Arg Leu Glu Arg Leu Ser Ala Glu Arg Ser Gln Lys Ala
 865 870 875 880

Thr Pro Gln Val Pro Val Leu Arg Gly Pro Pro Ala Pro Ala Pro Arg
 885 890 895

Val Ala Val Thr Ala Gln
 900

<210> 51

<211> 252

<212> PRT

<213> Homo sapiens

<400> 51

Met Arg Ala Pro Leu Leu Pro Pro Ala Pro Val Val Leu Ser Leu Leu
 1 5 10 15

Ile Leu Gly Ser Gly His Tyr Ala Ala Gly Leu Asp Leu Asn Asp Thr
 20 25 30

Tyr Ser Gly Lys Arg Glu Pro Phe Ser Gly Asp His Ser Ala Asp Gly
 35 40 45

Phe Glu Val Thr Ser Arg Ser Glu Met Ser Ser Gly Ser Glu Ile Ser
 50 55 60

Pro Val Ser Glu Met Pro Ser Ser Ser Glu Pro Ser Ser Gly Ala Asp
 65 70 75 80

Tyr Asp Tyr Ser Glu Glu Tyr Asp Asn Glu Pro Gln Ile Pro Gly Tyr
 85 90 95

Ile Val Asp Asp Ser Val Arg Val Glu Gln Val Val Lys Pro Pro Gln
 100 105 110

Asn Lys Thr Glu Ser Glu Asn Thr Ser Asp Lys Pro Lys Arg Lys Lys
 115 120 125

Lys Gly Gly Lys Asn Gly Lys Asn Arg Arg Asn Arg Lys Lys Lys Asn
 130 135 140

Pro Cys Asn Ala Glu Phe Gln Asn Phe Cys Ile His Gly Glu Cys Lys
 145 150 155 160

Tyr Ile Glu His Leu Glu Ala Val Thr Cys Lys Cys Gln Gln Glu Tyr
 165 170 175

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Phe	Gly	Glu	Arg	Cys	Gly	Glu	Lys	Ser	Met	Lys	Thr	His	Ser	Met	Ile
180							185							190	
Asp	Ser	Ser	Leu	Ser	Lys	Ile	Ala	Leu	Ala	Ala	Ile	Ala	Ala	Phe	Met
195						200								205	
Ser	Ala	Val	Ile	Leu	Thr	Ala	Val	Ala	Val	Ile	Thr	Val	Gln	Leu	Arg
210					215					220					
Arg	Gln	Tyr	Val	Arg	Lys	Tyr	Glu	Gly	Glu	Ala	Glu	Glu	Arg	Lys	Lys
225				230					235					240	
Leu	Arg	Gln	Glu	Asn	Gly	Asn	Val	His	Ala	Ile	Ala				
245				250											

<210> 52
<211> 271
<212> PRT
<213> Homo sapiens

<400> 52															
Met	Ala	Lys	Val	Pro	Asp	Met	Phe	Glu	Asp	Leu	Lys	Asn	Cys	Tyr	Ser
1			5					10						15	
Glu	Asn	Glu	Glu	Asp	Ser	Ser	Ser	Ile	Asp	His	Leu	Ser	Leu	Asn	Gln
20								25						30	
Lys	Ser	Phe	Tyr	His	Val	Ser	Tyr	Gly	Pro	Leu	His	Glu	Gly	Cys	Met
35							40							45	
Asp	Gln	Ser	Val	Ser	Leu	Ser	Ile	Ser	Glu	Thr	Ser	Lys	Thr	Ser	Lys
50							55					60			
Leu	Thr	Phe	Lys	Glu	Ser	Met	Val	Val	Val	Ala	Thr	Asn	Gly	Lys	Val
65							70				75			80	
Leu	Lys	Lys	Arg	Arg	Leu	Ser	Leu	Ser	Gln	Ser	Ile	Thr	Asp	Asp	Asp
85											90			95	
Leu	Glu	Ala	Ile	Ala	Asn	Asp	Ser	Glu	Glu	Ile	Ile	Lys	Pro	Arg	
100								105					110		
Ser	Ala	Pro	Phe	Ser	Phe	Leu	Ser	Asn	Val	Lys	Tyr	Asn	Phe	Met	Arg
115							120						125		
Ile	Ile	Lys	Tyr	Glu	Phe	Ile	Leu	Asn	Asp	Ala	Leu	Asn	Gln	Ser	Ile
130							135						140		
Ile	Arg	Ala	Asn	Asp	Gln	Tyr	Leu	Thr	Ala	Ala	Leu	His	Asn	Leu	
145							150					155		160	
Asp	Glu	Ala	Val	Lys	Phe	Asp	Met	Gly	Ala	Tyr	Lys	Ser	Ser	Lys	Asp
165								170						175	
Asp	Ala	Lys	Ile	Thr	Val	Ile	Leu	Arg	Ile	Ser	Lys	Thr	Gln	Leu	Tyr
180								185						190	

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Val Thr Ala Gln Asp Glu Asp Gln Pro Val Leu Leu Lys Glu Met Pro
 195 200 205

Glu Ile Pro Lys Thr Ile Thr Gly Ser Glu Thr Asn Leu Leu Phe Phe
 210 215 220

Trp Glu Thr His Gly Thr Lys Asn Tyr Phe Thr Ser Val Ala His Pro
 225 230 235 240

Asn Leu Phe Ile Ala Thr Lys Gln Asp Tyr Trp Val Cys Leu Ala Gly
 245 250 255

Gly Pro Pro Ser Ile Thr Asp Phe Gln Ile Leu Glu Asn Gln Ala
 260 265 270

<210> 53

<211> 269

<212> PRT

<213> Homo sapiens

<400> 53

Met Ala Glu Val Pro Glu Leu Ala Ser Glu Met Met Ala Tyr Tyr Ser
 1 5 10 15

Gly Asn Glu Asp Asp Leu Phe Phe Glu Ala Asp Gly Pro Lys Gln Met
 20 25 30

Lys Cys Ser Phe Gln Asp Leu Asp Leu Cys Pro Leu Asp Gly Gly Ile
 35 40 45

Gln Leu Arg Ile Ser Asp His His Tyr Ser Lys Gly Phe Arg Gln Ala
 50 55 60

Ala Ser Val Val Val Ala Met Asp Lys Leu Arg Lys Met Leu Val Pro
 65 70 75 80

Cys Pro Gln Thr Phe Gln Glu Asn Asp Leu Ser Thr Phe Phe Pro Phe
 85 90 95

Ile Phe Glu Glu Glu Pro Ile Phe Phe Asp Thr Trp Asp Asn Glu Ala
 100 105 110

Tyr Val His Asp Ala Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp
 115 120 125

Ser Gln Gln Lys Ser Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala
 130 135 140

Leu His Leu Gln Gly Gln Asp Met Glu Gln Gln Val Val Phe Ser Met
 145 150 155 160

Ser Phe Val Gln Gly Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu
 165 170 175

Gly Leu Lys Glu Lys Asn Leu Tyr Leu Ser Cys Val Leu Lys Asp Asp
 180 185 190

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Lys Pro Thr Leu Gln Leu Glu Ser Val Asp Pro Lys Asn Tyr Pro Lys
 195 200 205

Lys Lys Met Glu Lys Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn
 210 215 220

Lys Leu Glu Phe Glu Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr
 225 230 235 240

Ser Gln Ala Glu Asn Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly
 245 250 255

Gln Asp Ile Thr Asp Phe Thr Met Gln Phe Val Ser Ser
 260 265

<210> 54

<211> 153

<212> PRT

<213> Homo sapiens

<400> 54

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
 1 5 10 15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
 20 25 30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
 35 40 45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
 50 55 60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
 65 70 75 80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
 85 90 95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
 100 105 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
 115 120 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
 130 135 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
 145 150

<210> 55

<211> 125

<212> PRT

<213> Homo sapiens

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<400> 55

Met	Lys	Lys	Ser	Gly	Val	Leu	Phe	Leu	Leu	Gly	Ile	Ile	Leu	Leu	Val
1				5				10						15	

Leu	Ile	Gly	Val	Gln	Gly	Thr	Pro	Val	Val	Arg	Lys	Gly	Arg	Cys	Ser
						20		25					30		

Cys	Ile	Ser	Thr	Asn	Gln	Gly	Thr	Ile	His	Leu	Gln	Ser	Leu	Lys	Asp
						35		40				45			

Leu	Lys	Gln	Phe	Ala	Pro	Ser	Pro	Ser	Cys	Glu	Lys	Ile	Glu	Ile	Ile
						50		55			60				

Ala	Thr	Leu	Lys	Asn	Gly	Val	Gln	Thr	Cys	Leu	Asn	Pro	Asp	Ser	Ala
						65		70			75		80		

Asp	Val	Lys	Glu	Leu	Ile	Lys	Lys	Trp	Glu	Lys	Gln	Val	Ser	Gln	Lys
						85			90			95			

Lys	Lys	Gln	Lys	Asn	Gly	Lys	Lys	His	Gln	Lys	Lys	Val	Leu	Lys
						100		105			110			

Val	Arg	Lys	Ser	Gln	Arg	Ser	Arg	Gln	Lys	Lys	Thr	Thr		
						115		120			125			

<210> 56

<211> 210

<212> PRT

<213> Homo sapiens

<400> 56

Met	Leu	Pro	Leu	Pro	Ser	Cys	Ser	Leu	Pro	Ile	Leu	Leu	Phe	Leu
1						5				10			15	

Leu	Pro	Ser	Val	Pro	Ile	Glu	Ser	Gln	Pro	Pro	Pro	Ser	Thr	Leu	Pro
						20		25				30			

Pro	Phe	Leu	Ala	Pro	Glu	Trp	Asp	Leu	Leu	Ser	Pro	Arg	Val	Val	Leu
						35		40			45				

Ser	Arg	Gly	Ala	Pro	Ala	Gly	Pro	Pro	Leu	Leu	Phe	Leu	Leu	Glu	Ala
						50		55			60				

Gly	Ala	Phe	Arg	Glu	Ser	Ala	Gly	Ala	Pro	Ala	Asn	Arg	Ser	Arg	Arg
						65		70			75		80		

Gly	Val	Ser	Glu	Thr	Ala	Pro	Ala	Ser	Arg	Arg	Gly	Glu	Leu	Ala	Val
						85		90			95				

Cys	Asp	Ala	Val	Ser	Gly	Trp	Val	Thr	Asp	Arg	Arg	Thr	Ala	Val	Asp
						100		105			110				

Leu	Arg	Gly	Arg	Glu	Val	Glu	Val	Leu	Gly	Glu	Val	Pro	Ala	Ala	Gly
						115		120			125				

Gly	Ser	Pro	Leu	Arg	Gln	Tyr	Phe	Phe	Glu	Thr	Arg	Cys	Lys	Ala	Asp
						130		135			140				

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Asn Ala Glu Glu Gly Gly Pro Gly Ala Gly Gly Gly Cys Arg Gly
 145 150 155 160

Val Asp Arg Arg His Trp Val Ser Glu Cys Lys Ala Lys Gln Ser Tyr
 165 170 175

Val Arg Ala Leu Thr Ala Asp Ala Gln Gly Arg Val Gly Trp Arg Trp
 180 185 190

Ile Arg Ile Asp Thr Ala Cys Val Cys Thr Leu Leu Ser Arg Thr Gly
 195 200 205

Arg Ala
 210

<210> 57

<211> 259

<212> PRT

<213> Homo sapiens

<400> 57

Met Ser Glu Val Pro Val Ala Arg Val Trp Leu Val Leu Leu Leu
 1 5 10 15

Thr Val Gln Val Gly Val Thr Ala Gly Ala Pro Trp Gln Cys Ala Pro
 20 25 30

Cys Ser Ala Glu Lys Leu Ala Leu Cys Pro Pro Val Ser Ala Ser Cys
 35 40 45

Ser Glu Val Thr Arg Ser Ala Gly Cys Gly Cys Cys Pro Met Cys Ala
 50 55 60

Leu Pro Leu Gly Ala Ala Cys Gly Val Ala Thr Ala Arg Cys Ala Arg
 65 70 75 80

Gly Leu Ser Cys Arg Ala Leu Pro Gly Glu Gln Gln Pro Leu His Ala
 85 90 95

Leu Thr Arg Gly Gln Gly Ala Cys Val Gln Glu Ser Asp Ala Ser Ala
 100 105 110

Pro His Ala Ala Glu Ala Gly Ser Pro Glu Ser Pro Glu Ser Thr Glu
 115 120 125

Ile Thr Glu Glu Leu Leu Asp Asn Phe His Leu Met Ala Pro Ser
 130 135 140

Glu Glu Asp His Ser Ile Leu Trp Asp Ala Ile Ser Thr Tyr Asp Gly
 145 150 155 160

Ser Lys Ala Leu His Val Thr Asn Ile Lys Lys Trp Lys Glu Pro Cys
 165 170 175

Arg Ile Glu Leu Tyr Arg Val Val Glu Ser Leu Ala Lys Ala Gln Glu
 180 185 190

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Thr Ser Gly Glu Glu Ile Ser Lys Phe Tyr Leu Pro Asn Cys Asn Lys
195 200 205

Asn Gly Phe Tyr His Ser Arg Gln Cys Glu Thr Ser Met Asp Gly Glu
210 215 220

Ala Gly Leu Cys Trp Cys Val Tyr Pro Trp Asn Gly Lys Arg Ile Pro
225 230 235 240

Gly Ser Pro Glu Ile Arg Gly Asp Pro Asn Cys Gln Ile Tyr Phe Asn
245 250 255

Val Gln Asn

<210> 58

<211> 107

<212> PRT

<213> Homo sapiens

<400> 58

Met Ala Arg Ala Thr Leu Ser Ala Ala Pro Ser Asn Pro Arg Leu Leu
1 5 10 15

Arg Val Ala Leu Leu Leu Leu Val Ala Ala Ser Arg Arg Ala
20 25 30

Ala Gly Ala Pro Leu Ala Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr
35 40 45

Leu Gln Gly Ile His Leu Lys Asn Ile Gln Ser Val Lys Val Lys Ser
50 55 60

Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn
65 70 75 80

Gly Gln Lys Ala Cys Leu Asn Pro Ala Ser Pro Met Val Lys Lys Ile
85 90 95

Ile Glu Lys Met Leu Lys Asn Gly Lys Ser Asn
100 105

<210> 59

<211> 455

<212> PRT

<213> Homo sapiens

<400> 59

Met Gly Leu Ser Thr Val Pro Asp Leu Leu Pro Leu Val Leu Leu
1 5 10 15

Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
20 25 30

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His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys
35 40 45

Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
50 55 60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
65 70 75 80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
85 90 95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
100 105 110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
115 120 125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
130 135 140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
145 150 155 160

Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
165 170 175

Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
180 185 190

Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
195 200 205

Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu
210 215 220

Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp Lys
225 230 235 240

Ser Lys Leu Tyr Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu
245 250 255

Gly Glu Leu Glu Gly Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser
260 265 270

Phe Ser Pro Thr Pro Gly Phe Thr Pro Thr Leu Gly Phe Ser Pro Val
275 280 285

Pro Ser Ser Thr Phe Thr Ser Ser Ser Thr Tyr Thr Pro Gly Asp Cys
290 295 300

Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro Pro Tyr Gln Gly
305 310 315 320

Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile Pro Asn
325 330 335

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Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp
 340 345 350

Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro
 355 360 365

Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu
 370 375 380

Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln
 385 390 395 400

Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala
 405 410 415

Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly
 420 425 430

Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro
 435 440 445

Pro Ala Pro Ser Leu Leu Arg
 450 455

<210> 60

<211> 235

<212> PRT

<213> Homo sapiens

<400> 60

Met Thr Val

1

	20	25	30
Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu			
35	40	45	
Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu			
50	55	60	
Gln Asp Glu Glu Leu Cys Gly Ala Leu Trp Arg Leu Val Leu Ala Gln			
65	70	75	80
Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly			
85	90	95	
Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala			
100	105	110	
Phe Gln Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser			
115	120	125	
Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp			
130	135	140	

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Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
 145 150 155 160

Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser Pro Arg Pro Leu Glu Ala
 165 170 175

Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu Leu Leu Leu Leu Leu
 180 185 190

Pro Val Gly Leu Leu Leu Ala Ala Ala Trp Cys Leu His Trp Gln
 195 200 205

Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly Glu Gln Val Pro Pro Val
 210 215 220

Pro Ser Pro Gln Asp Leu Leu Leu Val Glu His
 225 230 235

<210> 61

<211> 212

<212> PRT

<213> Homo sapiens

<400> 61

Met Asn Ser Phe Ser Thr Ser Ala Phe Gly Pro Val Ala Phe Ser Leu
 1 5 10 15

Gly Leu Leu Leu Val Leu Pro Ala Ala Phe Pro Ala Pro Val Pro Pro
 20 25 30

Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr
 35 40 45

Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile
 50 55 60

Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser
 65 70 75 80

Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys Met Ala
 85 90 95

Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu
 100 105 110

Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr
 115 120 125

Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln
 130 135 140

Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn
 145 150 155 160

Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu
 165 170 175

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Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp Met Thr Thr His
 180 185 190

Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala
 195 200 205

Leu Arg Gln Met
 210

<210> 62

<211> 99

<212> PRT

<213> Homo sapiens

<400> 62

Met Lys Val Ser Ala Ala Leu Leu Cys Leu Leu Leu Ile Ala Ala Thr
 1 5 10 15

Phe Ile Pro Gln Gly Leu Ala Gln Pro Asp Ala Ile Asn Ala Pro Val
 20 25 30

Thr Cys Cys Tyr Asn Phe Thr Asn Arg Lys Ile Ser Val Gln Arg Leu
 35 40 45

Ala Ser Tyr Arg Arg Ile Thr Ser Ser Lys Cys Pro Lys Glu Ala Val
 50 55 60

Ile Phe Lys Thr Ile Val Ala Lys Glu Ile Cys Ala Asp Pro Lys Gln
 65 70 75 80

Lys Trp Val Gln Asp Ser Met Asp His Leu Asp Lys Gln Thr Gln Thr
 85 90 95

Pro Lys Thr

<210> 63

<211> 233

<212> PRT

<213> Homo sapiens

<400> 63

Met Ser Thr Glu Ser Met Ile Arg Asp Val Glu Leu Ala Glu Glu Ala
 1 5 10 15

Leu Pro Lys Lys Thr Gly Gly Pro Gln Gly Ser Arg Arg Cys Leu Phe
 20 25 30

Leu Ser Leu Phe Ser Phe Leu Ile Val Ala Gly Ala Thr Thr Leu Phe
 35 40 45

Cys Leu Leu His Phe Gly Val Ile Gly Pro Gln Arg Glu Glu Phe Pro
 50 55 60

Arg Asp Leu Ser Leu Ile Ser Pro Leu Ala Gln Ala Val Arg Ser Ser
 65 70 75 80

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Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro
 85 90 95

 Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu
 100 105 110

 Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser
 115 120 125

 Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly
 130 135 140

 Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala
 145 150 155 160

 Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro
 165 170 175

 Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu
 180 185 190

 Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu
 195 200 205

 Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly
 210 215 220

 Gln Val Tyr Phe Gly Ile Ile Ala Leu
 225 230

<210> 64
 <211> 94
 <212> PRT
 <213> Homo sapiens

<400> 64
 Met Ala Pro Leu Lys Met Leu Ala Leu Val Thr Leu Leu Leu Gly Ala
 1 5 10 15

 Ser Leu Gln His Ile His Ala Ala Arg Gly Thr Asn Val Gly Arg Glu
 20 25 30

 Cys Cys Leu Glu Tyr Phe Lys Gly Ala Ile Pro Leu Arg Lys Leu Lys
 35 40 45

 Thr Trp Tyr Gln Thr Ser Glu Asp Cys Ser Arg Asp Ala Ile Val Phe
 50 55 60

 Val Thr Val Gln Gly Arg Ala Ile Cys Ser Asp Pro Asn Asn Lys Arg
 65 70 75 80

 Val Lys Asn Ala Val Lys Tyr Leu Gln Ser Leu Glu Arg Ser
 85 90

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<210> 65

<211> 267

<212> PRT

<213> Homo sapiens

<400> 65

Met	Arg	Leu	Thr	Val	Leu	Cys	Ala	Val	Cys	Leu	Leu	Pro	Gly	Ser	Leu
1				5					10						15

Ala	Leu	Pro	Leu	Pro	Gln	Glu	Ala	Gly	Gly	Met	Ser	Glu	Leu	Gln	Trp
				20				25						30	

Glu	Gln	Ala	Gln	Asp	Tyr	Leu	Lys	Arg	Phe	Tyr	Leu	Tyr	Asp	Ser	Glu
				35			40					45			

Thr	Lys	Asn	Ala	Asn	Ser	Leu	Glu	Ala	Lys	Leu	Lys	Glu	Met	Gln	Lys
					50		55				60				

Phe	Phe	Gly	Leu	Pro	Ile	Thr	Gly	Met	Leu	Asn	Ser	Arg	Val	Ile	Glu
65					70				75					80	

Ile	Met	Gln	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp	Val	Ala	Glu	Tyr	Ser
					85			90					95		

Leu	Phe	Pro	Asn	Ser	Pro	Lys	Trp	Thr	Ser	Lys	Val	Val	Thr	Tyr	Arg
					100			105					110		

Ile	Val	Ser	Tyr	Thr	Arg	Asp	Leu	Pro	His	Ile	Thr	Val	Asp	Arg	Leu
					115			120				125			

Val	Ser	Lys	Ala	Leu	Asn	Met	Trp	Gly	Lys	Glu	Ile	Pro	Leu	His	Phe
					130			135			140				

Arg	Lys	Val	Val	Trp	Gly	Thr	Ala	Asp	Ile	Met	Ile	Gly	Phe	Ala	Arg
145					150					155			160		

Gly	Ala	His	Gly	Asp	Ser	Tyr	Pro	Phe	Asp	Gly	Pro	Gly	Asn	Thr	Leu
					165			170					175		

Ala	His	Ala	Phe	Ala	Pro	Gly	Thr	Gly	Leu	Gly	Gly	Asp	Ala	His	Phe
					180			185				190			

Asp	Glu	Asp	Glu	Arg	Trp	Thr	Asp	Gly	Ser	Ser	Leu	Gly	Ile	Asn	Phe
					195			200			205				

Leu	Tyr	Ala	Ala	Thr	His	Glu	Leu	Gly	His	Ser	Leu	Gly	Met	Gly	His
					210			215			220				

Ser	Ser	Asp	Pro	Asn	Ala	Val	Met	Tyr	Pro	Thr	Tyr	Gly	Asn	Gly	Asp
225						230				235			240		

Pro	Gln	Asn	Phe	Lys	Leu	Ser	Gln	Asp	Asp	Ile	Lys	Gly	Ile	Gln	Lys
					245			250			255				

Leu	Tyr	Gly	Lys	Arg	Ser	Asn	Ser	Arg	Lys	Lys					
					260			265							

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<210> 66

<211> 707

<212> PRT

<213> Homo sapiens

<400> 66

Met	Ser	Leu	Trp	Gln	Pro	Leu	Val	Leu	Val	Leu	Leu	Val	Leu	Gly	Cys
1						5			10						15

Cys	Phe	Ala	Ala	Pro	Arg	Gln	Arg	Gln	Ser	Thr	Leu	Val	Leu	Phe	Pro
									25						30

Gly	Asp	Leu	Arg	Thr	Asn	Leu	Thr	Asp	Arg	Gln	Leu	Ala	Glu	Glu	Tyr
									40						45

Leu	Tyr	Arg	Tyr	Gly	Tyr	Thr	Arg	Val	Ala	Glu	Met	Arg	Gly	Glu	Ser
								55				60			

Lys	Ser	Leu	Gly	Pro	Ala	Leu	Leu	Leu	Gln	Lys	Gln	Leu	Ser	Leu
65						70				75				80

Pro	Glu	Thr	Gly	Glu	Leu	Asp	Ser	Ala	Thr	Leu	Lys	Ala	Met	Arg	Thr
									85					90	

Pro	Arg	Cys	Gly	Val	Pro	Asp	Leu	Gly	Arg	Phe	Gln	Thr	Phe	Glu	Gly
								100				105			110

Asp	Leu	Lys	Trp	His	His	Asn	Ile	Thr	Tyr	Trp	Ile	Gln	Asn	Tyr
							115				120			125

Ser	Glu	Asp	Leu	Pro	Arg	Ala	Val	Ile	Asp	Asp	Ala	Phe	Ala	Arg	Ala
							130				135			140	

Phe	Ala	Leu	Trp	Ser	Ala	Val	Thr	Pro	Leu	Thr	Phe	Thr	Arg	Val	Tyr
							145				150			155	

Ser	Arg	Asp	Ala	Asp	Ile	Val	Ile	Gln	Phe	Gly	Val	Ala	Glu	His	Gly
							165				170			175	

Asp	Gly	Tyr	Pro	Phe	Asp	Gly	Lys	Asp	Gly	Leu	Leu	Ala	His	Ala	Phe
							180				185			190	

Pro	Pro	Gly	Pro	Gly	Ile	Gln	Gly	Asp	Ala	His	Phe	Asp	Asp	Asp	Glu
							195				200			205	

Leu	Trp	Ser	Leu	Gly	Lys	Gly	Val	Val	Val	Pro	Thr	Arg	Phe	Gly	Asn
							210				215			220	

Ala	Asp	Gly	Ala	Ala	Cys	His	Phe	Pro	Phe	Ile	Phe	Glu	Gly	Arg	Ser
							225				230			235	

Tyr	Ser	Ala	Cys	Thr	Thr	Asp	Gly	Arg	Ser	Asp	Gly	Leu	Pro	Trp	Cys
							245				250			255	

Ser	Thr	Thr	Ala	Asn	Tyr	Asp	Thr	Asp	Asp	Arg	Phe	Gly	Phe	Cys	Pro
							260				265			270	

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Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
 275 280 285
 Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
 290 295 300
 Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
 305 310 315 320
 Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
 325 330 335
 Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
 340 345 350
 Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
 355 360 365
 Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
 370 375 380
 Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
 385 390 395 400
 His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
 405 410 415
 Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
 420 425 430
 Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
 435 440 445
 Pro Glu Pro Arg Pro Pro Thr Thr Thr Pro Gln Pro Thr Ala Pro
 450 455 460
 Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
 465 470 475 480
 Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
 485 490 495
 Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
 500 505 510
 Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
 515 520 525
 Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
 530 535 540
 Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
 545 550 555 560
 Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
 565 570 575

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Lys Lys Leu Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
 580 585 590

Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
 595 600 605

Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
 610 615 620

Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
 625 630 635 640

Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
 645 650 655

Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
 660 665 670

Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
 675 680 685

Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
 690 695 700

Pro Glu Asp
 705

<210> 67
<211> 167
<212> PRT
<213> Homo sapiens

<400> 67
Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu
 1 5 10 15

Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys
 20 25 30

Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
 35 40 45

Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
 50 55 60

Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
 65 70 75 80

Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
 85 90 95

Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
 100 105 110

Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
 115 120 125

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Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
 130 135 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
 145 150 155 160

Leu Asp Leu Ser Pro Gly Cys
 165

<210> 68

<211> 2619

<212> DNA

<213> Homo sapiens

<400> 68

gactccttagg ggcttgcaga cctagtggga gagaagaac atcgcaagcag ccaggcagaa 60
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 gcctcaggcc tttcggagc ctggatcctc aagaacaag tagacctggc cgccccggagt 180
 ggggagggaa ggggtgtcta ttggcaaca gggggcaaa gccctgaata aaggggcgca 240
 gggcaggcgc aagtgcagag cttcggttg ccaagtcgcc tccagaccgc agacatgaaa 300
 ctgttcttcc tcgtcctgct gttcctcggt gcccctcgac tgggtctggc tggccgtagg 360
 agaaggagtg ttcagtggtg cgccgtatcc caacccgagg ccacaaaatg cttccaatgg 420
 caaagaata tgagaaaaatg gcgtggccct cctgtcagct gcataaaagag agactcccc 480
 atccagtgtt tccaggccat tgcggaaaac agggccgatg ctgtgaccct tggatgggt 540
 ttcatatacg aggccaggcct ggcccccattc aaactgcgc ac tggatcgcc ggaagtctac 600
 gggaccgaaa gacagccacg aactcaatat tatggcggtt ctgtgttgc gaaaggccggc 660
 agctttcagc tgaacgaact gcaaggctgc aagtccctgc acacaggccct tcgcaggacc 720
 gctggatggc atgtccctac agggacactt cgtccatttc tgaattggac ggggtccaccc 780
 gagcccatgg aggccaggctt ggccagggtt ttctcagcca gctgtgttcc cgggtgcagat 840
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 ttctcctccca aggaaccgtt cttcagctac tctgggtgcct tcaagtgtct gagagacggg 960
 gctggagacg tggctttat cagagagagc aagtgttttgc agacccgttgc agacgaggct 1020
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 ggcggggctg tgggtgtgc ggtggggcagc caggagctgc gcaagtgtaa ccagtggagt 1440
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 ctggtgctga aaggagaagc tggatgcattt agttggatg gaggatatgt gtacactgca 1560
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 tgc当地atgtt atgaatattt cagtccaaacgc tggcccttc ggtctgaccc gagatctaat 1860
 ctctgtgtct tggatgttttgc cggcggccatc ggtggatataa atcatggccgt ggtgtctcg 1920
 gagagataact acggctacac tggggcttc cgggtgcctgg ctggaaatgc tggagacgtt 1980
 gcattttgtga aagatgtcac tggatgtggc aacactgtatg gaaataacaa tgaggcatgg 2040
 gctaaggatt tggatgtggc agactttgcg ctgcgtgtgc tcgatggcaa acggaaagcc 2100
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 aatggatctg actgcggcga caagtttgc ttattccatgt ctgaaaccaa aacacttctg 2280
 ttcaatgaca acactgaggc tctggccaga ctccatggca aaacaacata tggaaaaatata 2340
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 aagcctcagc catcaactgc cccagctct tctcccccagg tggatggggg cttggctcc 2520

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cctgctgaag gtggggattt cccatccatc tgcttacaat tccctgctgt cgtcttagca 2580
 agaagtaaaa tgagaaattt tgttgatatt caaaaaaaaaa 2619

<210> 69
<211> 711
<212> PRT
<213> Homo sapiens

<400> 69
Met Lys Leu Val Phe Leu Val Leu Leu Phe Leu Gly Ala Leu Gly Leu
1 5 10 15

Cys Leu Ala Gly Arg Arg Arg Ser Val Gln Trp Cys Ala Val Ser
20 25 30

Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys
35 40 45

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
50 55 60

Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
65 70 75 80

Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
85 90 95

Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
100 105 110

Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
115 120 125

Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
130 135 140

Trp Asn Val Pro Thr Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
145 150 155 160

Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
165 170 175

Cys Val Pro Gly Ala Asp Lys Gly Gln Phe Pro Asn Leu Cys Arg Leu
180 185 190

Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
195 200 205

Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
210 215 220

Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
225 230 235 240

Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg
245 250 255

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Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
260 265 270

His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp
275 280 285

Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
290 295 300

Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
305 310 315 320

Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
325 330 335

Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
340 345 350

Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
355 360 365

Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
370 375 380

Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
385 390 395 400

Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
405 410 415

Gly Tyr Val Tyr Thr Ala Cys Lys Cys Gly Leu Val Pro Val Leu Ala
420 425 430

Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
435 440 445

Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
450 455 460

Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
465 470 475 480

Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
485 490 495

Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
500 505 510

Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
515 520 525

Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
530 535 540

Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
545 550 555 560

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Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
 565 570 575

Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
 580 585 590

Leu Leu Cys Leu Asp Gly Lys Arg Lys Pro Val Thr Glu Ala Arg Ser
 595 600 605

Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
 610 615 620

Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
 625 630 635 640

Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
 645 650 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
 660 665 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
 705 710

<210> 70

<211> 597

<212> DNA

<213> Homo sapiens

<400> 70

atgcccctag gtctcctgtg gctgggccta gccctgttgg gggctctgca tgcccaggcc 60
 caggactcca cctcagaccc gatcccagcc ccacctctga gcaagggtccc tctgcagcag 120
 aacctccagg acaaccaatt ccagggaaag tggtatgtgg taggcctggc agggaatgca 180
 attctcagag aagacaaaaga cccgc当地aaatgcca cc当地ctatga gctgaaagaaa 240
 gacaagagat acaatgtcac ctccgtctgt ttttagaaaa agaagtgtga ctactggatc 300
 aggacttttg ttccagggtt ccagccccgc gagttcacgc tggcaacat taagagttac 360
 cctggattaa cgagttaccc cgtccgagtg gtgagcacca actacaacca gcatgctatg 420
 gtgttcttca agaaagtttc tcaaaacagg gagtaacttca agatcaccct ctacgggaga 480
 accaaggagc tgacttcgga actaaaggag aacctcatcc gcttctccaa atatctgggc 540
 ctccctgaaa accacatcgt cttccctgtc ccaatcgacc agtgtatcga cggctga 597

<210> 71

<211> 198

<212> PRT

<213> Homo sapiens

<400> 71

Met Pro Leu Gly Leu Leu Trp Leu Gly Leu Ala Leu Leu Gly Ala Leu
 1 5 10 15

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His	Ala	Gln	Ala	Gln	Asp	Ser	Thr	Ser	Asp	Leu	Ile	Pro	Ala	Pro	Pro
					20				25				30		
Leu	Ser	Lys	Val	Pro	Leu	Gln	Gln	Asn	Phe	Gln	Asp	Asn	Gln	Phe	Gln
					35			40				45			
Gly	Lys	Trp	Tyr	Val	Val	Gly	Leu	Ala	Gly	Asn	Ala	Ile	Leu	Arg	Glu
					50			55			60				
Asp	Lys	Asp	Pro	Gln	Lys	Met	Tyr	Ala	Thr	Ile	Tyr	Glu	Leu	Lys	Glu
					65			70			75			80	
Asp	Lys	Ser	Tyr	Asn	Val	Thr	Ser	Val	Leu	Phe	Arg	Lys	Lys	Cys	
					85				90			95			
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					115			120			125				
Arg	Val	Val	Ser	Thr	Asn	Tyr	Asn	Gln	His	Ala	Met	Val	Phe	Phe	Lys
					130			135			140				
Lys	Val	Ser	Gln	Asn	Arg	Glu	Tyr	Phe	Lys	Ile	Thr	Leu	Tyr	Gly	Arg
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Thr	Lys	Glu	Leu	Thr	Ser	Glu	Leu	Lys	Glu	Asn	Phe	Ile	Arg	Phe	Ser
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Lys	Tyr	Leu	Gly	Leu	Pro	Glu	Asn	His	Ile	Val	Phe	Pro	Val	Pro	Ile
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<210> 72
<211> 2334
<212> DNA
<213> Homo sapiens

<400> 72
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<211> 2116
<212> DNA
<213> Homo s

<400> 73
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gagattcagt tttcatttgt tcattaattc tataaggcca taaaacaggt aatataaaaa 720
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<210> 74
<211> 80
<212> PRT
<213> Homo sapiens

<400> 74
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Thr Ser Ser Asn Ser Ser Gln Ser Thr Ser Asn Ser Gly Leu Ala Pro
35 40 45
Asn Pro Thr Asn Ala Thr Thr Lys Ala Ala Gly Gly Ala Leu Gln Ser
50 55 60
Thr Ala Ser Leu Phe Val Val Ser Leu Ser Leu Leu His Leu Tyr Ser
65 70 75 80

<210> 75
<211> 1864
<212> DNA
<213> Homo sapiens

<400> 75
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gctgttattt ttctcaatac gaggcgcaag gtggactggc tgactgagaa gatgcattgc 900

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<210> 76
<211> 407
<212> PRT
<213> Homo sapiens

<400> 76

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Asp Asn Phe Asp Asp Met Asn Leu Lys Glu Ser Leu Leu Arg Gly Ile
35 40 45

Tyr Ala Tyr Gly Phe Glu Lys Pro Ser Ala Ile Gln Gln Arg Ala Ile
 50 55 60

Ile Pro Cys Ile Lys Gly Tyr Asp Val Ile Ala Gln Ala Gln Ser Gly
65 70 75 80

Thr Gly Lys Thr Ala Thr Phe Ala Ile Ser Ile Leu Gln Gln Leu Glu
85 90 95

Ile Glu Phe Lys Glu Thr Gln Ala Leu Val Leu Ala Pro Thr Arg Glu
100 105 110

Leu Ala Gln Gln Ile Gln Lys Val Ile Leu Ala Leu Gly Asp Tyr Met
115 120 125

Gly Ala Thr Cys His Ala Cys Ile Gly Gly Thr Asn Val Arg Asn Glu
130 135 140

Met Gln Lys Leu Gln Ala Glu Ala Pro His Ile Val Val Gly Thr Pro
145 150 155 160

Gly Arg Val Phe Asp Met Leu Asn Arg Arg Tyr Leu Ser Pro Lys Trp
165 170 175

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Ile Lys Met Phe Val Leu Asp Glu Ala Asp Glu Met Leu Ser Arg Gly
 180 185 190

Phe Lys Asp Gln Ile Tyr Glu Ile Phe Gln Lys Leu Asn Thr Ser Ile
 195 200 205

Gln Val Val Phe Ala Ser Ala Thr Met Pro Thr Asp Val Leu Glu Val
 210 215 220

Thr Lys Lys Phe Met Arg Asp Pro Ile Arg Ile Leu Val Lys Lys Glu
 225 230 235 240

Glu Leu Thr Leu Glu Gly Ile Lys Gln Phe Tyr Ile Asn Val Glu Arg
 245 250 255

Glu Glu Trp Lys Leu Asp Thr Leu Cys Asp Leu Tyr Glu Thr Leu Thr
 260 265 270

Ile Thr Gln Ala Val Ile Phe Leu Asn Thr Arg Arg Lys Val Asp Trp
 275 280 285

Leu Thr Glu Lys Met His Ala Arg Asp Phe Thr Val Ser Ala Leu His
 290 295 300

Gly Asp Met Asp Gln Lys Glu Arg Asp Val Ile Met Arg Glu Phe Arg
 305 310 315 320

Ser Gly Ser Ser Arg Val Leu Ile Thr Thr Asp Leu Leu Ala Arg Gly
 325 330 335

Ile Asp Val Gln Gln Val Ser Leu Val Ile Asn Tyr Asp Leu Pro Thr
 340 345 350

Asn Arg Glu Asn Tyr Ile His Arg Ile Gly Arg Gly Gly Arg Phe Gly
 355 360 365

Arg Lys Gly Val Ala Ile Asn Phe Val Thr Glu Glu Asp Lys Arg Ile
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Leu Arg Asp Ile Glu Thr Phe Tyr Asn Thr Thr Val Glu Glu Met Pro
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Met Asn Val Ala Asp Leu Ile
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<210> 77

<211> 1670

<212> DNA

<213> Homo sapiens

<400> 77

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 <211> 352
 <212> PRT
 <213> Homo sapiens

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Asn Ala Asn Phe Asn Lys Ile Phe Leu Pro Thr Ile Tyr Ser Ile Ile
 35 40 45

Phe Leu Thr Gly Ile Val Gly Asn Gly Leu Val Ile Leu Val Met Gly
 50 55 60

Tyr Gln Lys Lys Leu Arg Ser Met Thr Asp Lys Tyr Arg Leu His Leu
 65 70 75 80

Ser Val Ala Asp Leu Leu Phe Val Ile Thr Leu Pro Phe Trp Ala Val
 85 90 95

Asp Ala Val Ala Asn Trp Tyr Phe Gly Asn Phe Leu Cys Lys Ala Val
 100 105 110

His Val Ile Tyr Thr Val Asn Leu Tyr Ser Ser Val Leu Ile Leu Ala
 115 120 125

Phe Ile Ser Leu Asp Arg Tyr Leu Ala Ile Val His Ala Thr Asn Ser
 130 135 140

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Gln Arg Pro Arg Lys Leu Leu Ala Glu Lys Val Val Tyr Val Gly Val
 145 150 155 160

Trp Ile Pro Ala Leu Leu Leu Thr Ile Pro Asp Phe Ile Phe Ala Asn
 165 170 175

Val Ser Glu Ala Asp Asp Arg Tyr Ile Cys Asp Arg Phe Tyr Pro Asn
 180 185 190

Asp Leu Trp Val Val Val Phe Gln Phe Gln His Ile Met Val Gly Leu
 195 200 205

Ile Leu Pro Gly Ile Val Ile Leu Ser Cys Tyr Cys Ile Ile Ile Ser
 210 215 220

Lys Leu Ser His Ser Lys Gly His Gln Lys Arg Lys Ala Leu Lys Thr
 225 230 235 240

Thr Val Ile Leu Ile Leu Ala Phe Phe Ala Cys Trp Leu Pro Tyr Tyr
 245 250 255

Ile Gly Ile Ser Ile Asp Ser Phe Ile Leu Leu Glu Ile Ile Lys Gln
 260 265 270

Gly Cys Glu Phe Glu Asn Thr Val His Lys Trp Ile Ser Ile Thr Glu
 275 280 285

Ala Leu Ala Phe Phe His Cys Cys Leu Asn Pro Ile Leu Tyr Ala Phe
 290 295 300

Leu Gly Ala Lys Phe Lys Thr Ser Ala Gln His Ala Leu Thr Ser Val
 305 310 315 320

Ser Arg Gly Ser Ser Leu Lys Ile Leu Ser Lys Gly Lys Arg Gly Gly
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<210> 79
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 <212> DNA
 <213> Homo sapiens

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 <223> n is a, c, g, or t

<220>
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<220>
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<222> (897)..(897)
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<400> 79

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<211> 49
<212> PRT
<213> Homo sapiens

<400> 80

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Phe															
Asp															
Lys															
Ala															
Leu															
Lys															
Lys															
Thr															
Glu															
Thr															
Ile															
Glu															
Gln															
Glu															
Lys															
Arg															
Ser															
Glu															
Ile															

Ser

<210> 81
<211> 1198
<212> DNA
<213> Homo sapiens

<400> 81

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gcattttga gcaatgggg aacgctcacgg actgtgtggt aatgagagat ccaaacacca 180
agcgctctag gggcttggg tttgtcacat atgccactgt ggaggaggtg gatgcagcta 240
tgaatgcaag gccacacaag gtggatggaa gagttgtgga accaaagaga gctgtctcca 300
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gagaagattc tcaaagacca ggtgccact taactgtgaa aaagatattt gttggggca 360
 ttaaagaaga cactgaagaa catcacctaa gagattattt tgaacagtat gaaaaattt 420
 aagtgattga aatcatgact gaccgaggca gtggcaagaa aaggggctt gccttgcataa 480
 ccttgacga ccatgactcc gtggataaga ttgtcattca gaaataccat actgtgaatg 540
 gccacaactg tgaagttaga aaagccctgt caaagcaaga gatggctagt gcttcatcca 600
 gccaaagagg tcgaagtgg tctggaaact ttgggtggg tcgtggaggt gtttcggg 660
 gaaatgacaa ctccggcgt ggagggaaact tcagtggctcg tggcgctt ggtggcagcc 720
 gtgggtggg tggatatggg ggcagtgggg atggctataa tggattggc aatgatggaa 780
 gcaattttgg aggtgggtgg agctacaatg attttggaa ttacaacaat cagtcttcaa 840
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 ctcttaaaaa cagaaactca tctgtccaag ttcgtggcag aaaggaacgt ctttgtgaag 1080
 acctttatct gagccactgt acttcgttat cacggccatgc agtttacatg agctgttctg 1140
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<210> 82

<211> 320

<212> PRT

<213> Homo sapiens

<400> 82

Met	Ser	Lys	Ser	Glu	Ser	Pro	Lys	Glu	Pro	Gln	Leu	Arg	Lys	Leu
1														15

Phe	Ile	Gly	Gly	Leu	Ser	Phe	Glu	Thr	Thr	Asp	Glu	Ser	Leu	Arg	Ser
															30
				20				25							

His	Phe	Glu	Gln	Trp	Gly	Thr	Leu	Thr	Asp	Cys	Val	Val	Met	Arg	Asp
															45
				35				40							

Pro	Asn	Thr	Lys	Arg	Ser	Arg	Gly	Phe	Gly	Phe	Val	Thr	Tyr	Ala	Thr
															50
								55							60

Val	Glu	Glu	Val	Asp	Ala	Ala	Met	Asn	Ala	Arg	Pro	His	Lys	Val	Asp
															65
								70							80

Gly	Arg	Val	Val	Glu	Pro	Lys	Arg	Ala	Val	Ser	Arg	Glu	Asp	Ser	Gln
															85
									90						95

Arg	Pro	Gly	Ala	His	Leu	Thr	Val	Lys	Lys	Ile	Phe	Val	Gly	Gly	Ile
															100
									105						110

Lys	Glu	Asp	Thr	Glu	Glu	His	His	Leu	Arg	Asp	Tyr	Phe	Glu	Gln	Tyr
															115
									120						125

Gly	Lys	Ile	Glu	Val	Ile	Glu	Ile	Met	Thr	Asp	Arg	Gly	Ser	Gly	Lys
															130
									135						140

Lys	Arg	Gly	Phe	Ala	Phe	Val	Thr	Phe	Asp	Asp	His	Asp	Ser	Val	Asp
															145
									150						160

Lys	Ile	Val	Ile	Gln	Lys	Tyr	His	Thr	Val	Asn	Gly	His	Asn	Cys	Glu
															165
										170					175

Val	Arg	Lys	Ala	Leu	Ser	Lys	Gln	Glu	Met	Ala	Ser	Ala	Ser	Ser	Ser
															180
										185					190

Gln Arg Gly Arg Ser Gly Ser Gly Asn Phe Gly Gly Gly Arg Gly Gly
 195 200 205

Gly Phe Gly Gly Asn Asp Asn Phe Gly Arg Gly Gly Asn Phe Ser Gly
 210 215 220

Arg Gly Gly Phe Gly Gly Ser Arg Gly Gly Gly Tyr Gly Ser
 225 230 235 240

Gly Asp Gly Tyr Asn Gly Phe Gly Asn Asp Gly Ser Asn Phe Gly Gly
 245 250 255

Gly Gly Ser Tyr Asn Asp Phe Gly Asn Tyr Asn Asn Gln Ser Ser Asn
 260 265 270

Phe Gly Pro Met Lys Gly Gly Asn Phe Gly Gly Arg Ser Ser Gly Pro
 275 280 285

Tyr Gly Gly Gly Gln Tyr Phe Ala Lys Pro Arg Asn Gln Gly Gly
 290 295 300

Tyr Gly Gly Ser Ser Ser Ser Ser Tyr Gly Ser Gly Arg Arg Phe
 305 310 315 320

<210> 83
<211> 1125
<212> DNA
<213> Homo sapiens

<400> 83
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ctcttcttct tcgtcctcg cagcctgatc ttctgcttcg gcatctggat cctcatcgac 180
aagaccagct tcgtgcctt tggggcttg gccttcgtgc ctctgcagat ctggtccaaa 240
gtcctggcca tctcaggaat cttcaccatg ggcatcgccc tcctgggttg tggggggcc 300
ctcaaggagc tccgctgcct cctgggcctg tattttggga tgctgctgct cctgtttgcc 360
acacagatca ccctggaaat cctcatctcc actcagcgcc cccagctgga gcgaaacctg 420
cgggacgtcg tagaaaaaac catccaaaag tacggcacca accccgagga gaccgcggcc 480
gaggagagct gggactatgt gcagttccag ctgcgtgtct gggctggca ctacccgcag 540
gactggttcc aagtccatcat cctgagaggt aacgggtcg aggccgaccg cgtccccgtc 600
tcctgctaca acttgtcgcc gaccaacgac tccacaatcc tagataaggt gatcttgccc 660
cagctcagca ggcttggaca cctggcgccg tccagacaca gtgcagacat ctgcgtgtc 720
cctgcagaga gccacatcta ccgcgaggcc tgccgcgcagg gcctccagaa gtggctgcac 780
aacaacctta tttccatagt gggcatttgc ctgggcgtcg gcctactcga gctcgggttc 840
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taccgttagg ccccgccctc cccaaagtcc cgccccgccc ccgtcacgtg cgctgggcac 960
ttccctgctg cctgtaaata tttgttaat ccccaagttcg cctggagccc tccgccttca 1020
cattccctctg gggaccacg tggctgcgtg cccctgctgc tgtcacctct cccacgggac 1080
ctggggcttt cgtccacacg ttcctgtccc catctgtcg 1125

<210> 84
<211> 281

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<212> PRT

<213> Homo sapiens

<400> 84

Met	Ser	Ala	Gln	Glu	Ser	Cys	Leu	Ser	Leu	Ile	Lys	Tyr	Phe	Leu	Phe
1				5					10						15

Val	Phe	Asn	Leu	Phe	Phe	Val	Leu	Gly	Ser	Leu	Ile	Phe	Cys	Phe
			20				25						30	

Gly	Ile	Trp	Ile	Leu	Ile	Asp	Lys	Thr	Ser	Phe	Val	Ser	Phe	Val	Gly
	35					40						45			

Leu	Ala	Phe	Val	Pro	Leu	Gln	Ile	Trp	Ser	Lys	Val	Leu	Ala	Ile	Ser
50					55					60					

Gly	Ile	Phe	Thr	Met	Gly	Ile	Ala	Leu	Leu	Gly	Cys	Val	Gly	Ala	Leu
65					70				75				80		

Lys	Glu	Leu	Arg	Cys	Leu	Leu	Gly	Leu	Tyr	Phe	Gly	Met	Leu	Leu	Leu
					85			90				95			

Leu	Phe	Ala	Thr	Gln	Ile	Thr	Leu	Gly	Ile	Leu	Ile	Ser	Thr	Gln	Arg
				100			105					110			

Ala	Gln	Leu	Glu	Arg	Ser	Leu	Arg	Asp	Val	Val	Glu	Lys	Thr	Ile	Gln
					115			120				125			

Lys	Tyr	Gly	Thr	Asn	Pro	Glu	Glu	Thr	Ala	Ala	Glu	Glu	Ser	Trp	Asp
	130				135					140					

Tyr	Val	Gln	Phe	Gln	Leu	Arg	Cys	Cys	Gly	Trp	His	Tyr	Pro	Gln	Asp
	145				150				155			160			

Trp	Phe	Gln	Val	Leu	Ile	Leu	Arg	Gly	Asn	Gly	Ser	Glu	Ala	His	Arg
					165			170				175			

Val	Pro	Cys	Ser	Cys	Tyr	Asn	Leu	Ser	Ala	Thr	Asn	Asp	Ser	Thr	Ile
						180		185				190			

Leu	Asp	Lys	Val	Ile	Leu	Pro	Gln	Leu	Ser	Arg	Leu	Gly	His	Leu	Ala
					195			200				205			

Arg	Ser	Arg	His	Ser	Ala	Asp	Ile	Cys	Ala	Val	Pro	Ala	Glu	Ser	His
	210					215					220				

Ile	Tyr	Arg	Glu	Gly	Cys	Ala	Gln	Gly	Leu	Gln	Lys	Trp	Leu	His	Asn
225					230				235			240			

Asn	Leu	Ile	Ser	Ile	Val	Gly	Ile	Cys	Leu	Gly	Val	Gly	Leu	Leu	Glu
					245			250			255				

Leu	Gly	Phe	Met	Thr	Leu	Ser	Ile	Phe	Leu	Cys	Arg	Asn	Leu	Asp	His
				260				265				270			

Val	Tyr	Asn	Arg	Leu	Ala	Arg	Tyr	Arg							
				275			280								

<210> 85
<211> 1216
<212> DNA
<213> Homo sapiens

<400> 85
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ggtgctgagc tccccactgg ctttggctgg ggacacccga ccatgtttct tgcagcagga 180
taagtatgag tgcatttct tcaacggac ggagcgggtg cggttccctgc acagaggcat 240
ctataaccaa caggagaacg tgcgcttgc cagcgacgtg ggggaggtacc gggcggtgac 300
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gcgggcccgcg gtggacacct actgcagaca caactacggg gctgtggaga gcttcacagt 420
gcagcggcga gttgagccta aggtgactgt gtatcctgca aggaccaga ccctgcagca 480
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gttccggaac ggccaggaag agaaggctgg ggtgtgtcc acaggcctga ttcagaatgg 600
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cacctgccaa gtggagcacc caagcgtgac gagccctctc acagtggaaat ggagagcaca 720
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tggcaccaaa gacaaa 1216

<210> 86
<211> 266
<212> PRT
<213> Homo sapiens

<400> 86
Met Val Cys Leu Lys Leu Pro Gly Gly Ser Tyr Met Ala Val Leu Thr
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Val Thr Leu Met Val Leu Ser Ser Pro Leu Ala Leu Ala Gly Asp Thr
20 25 30
Arg Pro Cys Phe Leu Gln Gln Asp Lys Tyr Glu Cys His Phe Phe Asn
35 40 45
Gly Thr Glu Arg Val Arg Phe Leu His Arg Gly Ile Tyr Asn Gln Gln
50 55 60
Glu Asn Val Arg Phe Asp Ser Asp Val Gly Glu Tyr Arg Ala Val Thr
65 70 75 80
Glu Leu Gly Arg Pro Asp Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile
85 90 95
Leu Glu Gln Ala Arg Ala Ala Val Asp Thr Tyr Cys Arg His Asn Tyr
100 105 110

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Gly Ala Val Glu Ser Phe Thr Val Gln Arg Arg Val Glu Pro Lys Val
 115 120 125

Thr Val Tyr Pro Ala Arg Thr Gln Thr Leu Gln His His Asn Leu Leu
 130 135 140

Val Cys Ser Val Asn Gly Phe Tyr Pro Gly Ser Ile Glu Val Arg Trp
 145 150 155 160

Phe Arg Asn Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu
 165 170 175

Ile Gln Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Thr
 180 185 190

Val Pro Arg Ser Gly Glu Val Tyr Thr Cys Gln Val Glu His Pro Ser
 195 200 205

Val Thr Ser Pro Leu Thr Val Glu Trp Arg Ala Gln Ser Glu Ser Ala
 210 215 220

Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu Gly Leu Leu
 225 230 235 240

Phe Leu Gly Ala Gly Leu Phe Ile Tyr Phe Lys Asn Gln Lys Gly His
 245 250 255

Ser Gly Leu His Pro Thr Gly Leu Val Ser
 260 265

<210> 87

<211> 1881

<212> DNA

<213> Homo sapiens

<400> 87

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ttcagcaaag gagatcggtc aggaaaggtt gcagacttggc caggagccac ataccaagat 240
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gaaagataca acttccccaa cccaaacccg ttgtggagg acgacatgga taagaatgaa 1140
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gtccgttggc agcacatgg cgtcatgact ggagccaacg gggaaatgtc cttcatcaac 1260

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atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgaactg gcgtcagaag 1320
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 gcccgggtgga cctgcgtgtc tttgctgct ggatctgagtc acctcaagct tggttatgtc 1440
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 ttaaaaaaaaaaaaaaa aaaaaaaaaa a 1881

<210> 88

<211> 548

<212> PRT

<213> Homo sapiens

<400> 88

Met	Ala	Lys	Phe	Met	Thr	Pro	Val	Ile	Gln	Asp	Asn	Pro	Ser	Gly	Trp
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Gly	Pro	Cys	Ala	Val	Pro	Glu	Gln	Phe	Arg	Asp	Met	Pro	Tyr	Gln	Pro
															30
20								25							

Phe	Ser	Lys	Gly	Asp	Arg	Leu	Gly	Lys	Val	Ala	Asp	Trp	Thr	Gly	Ala
															45
35						40									

Thr	Tyr	Gln	Asp	Lys	Arg	Tyr	Thr	Asn	Lys	Tyr	Ser	Ser	Gln	Phe	Gly
															60
50						55									

Gly	Gly	Ser	Gln	Tyr	Ala	Tyr	Phe	His	Glu	Glu	Asp	Glu	Ser	Ser	Phe
															80
65					70				75						

Gln	Leu	Val	Asp	Thr	Ala	Arg	Thr	Gln	Lys	Thr	Ala	Tyr	Gln	Arg	Asn
															95
85									90						

Arg	Met	Arg	Phe	Ala	Gln	Arg	Asn	Leu	Arg	Arg	Asp	Lys	Asp	Arg	Arg
															110
100								105							

Asn	Met	Leu	Gln	Phe	Asn	Leu	Gln	Ile	Leu	Pro	Lys	Ser	Ala	Lys	Gln
															125
115						120									

Lys	Glu	Arg	Glu	Arg	Ile	Arg	Leu	Gln	Lys	Lys	Phe	Gln	Lys	Gln	Phe
															140
130							135								

Gly	Val	Arg	Gln	Lys	Trp	Asp	Gln	Lys	Ser	Gln	Lys	Pro	Arg	Asp	Ser
															160
145					150				155						

Ser	Val	Glu	Val	Arg	Ser	Asp	Trp	Glu	Val	Lys	Glu	Glu	Met	Asp	Phe
															175
165							170								

Pro	Gln	Leu	Met	Lys	Met	Arg	Tyr	Leu	Glu	Val	Ser	Glu	Pro	Gln	Asp
															190
180								185							

Ile	Glu	Cys	Cys	Gly	Ala	Leu	Glu	Tyr	Tyr	Asp	Lys	Ala	Phe	Asp	Arg
															205
195							200				205				

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Ile Thr Thr Arg Ser Glu Lys Pro Leu Arg Ser Ile Lys Arg Ile Phe
210 215 220

His Thr Val Thr Thr Asp Asp Pro Val Ile Arg Lys Leu Ala Lys
225 230 235 240

Thr Gln Gly Asn Val Phe Ala Thr Asp Ala Ile Leu Ala Thr Leu Met
245 250 255

Ser Cys Thr Arg Ser Val Tyr Ser Trp Asp Ile Val Val Gln Arg Val
260 265 270

Gly Ser Lys Leu Phe Phe Asp Lys Arg Asp Asn Ser Asp Phe Asp Leu
275 280 285

Leu Thr Val Ser Glu Thr Ala Asn Glu Pro Pro Gln Asp Glu Gly Asn
290 295 300

Ser Phe Asn Ser Pro Arg Asn Leu Ala Met Glu Ala Thr Tyr Ile Asn
305 310 315 320

His Asn Phe Ser Gln Gln Cys Leu Arg Met Gly Lys Glu Arg Tyr Asn
325 330 335

Phe Pro Asn Pro Asn Pro Phe Val Glu Asp Asp Met Asp Lys Asn Glu
340 345 350

Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys Leu Gly Asp Asp
355 360 365

Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val Met Thr Gly Ala
370 375 380

Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu Asn Glu Trp Asp
385 390 395 400

Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys Leu Asp Ser Gln
405 410 415

Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn Ser Tyr Lys Leu
420 425 430

Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser Glu Tyr Leu Lys
435 440 445

Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser Ser Arg His Val
450 455 460

Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe Ala Ser Gln Ile
465 470 475 480

Asn Leu Ser Val Glu Asn Ala Trp Gly Ile Leu Arg Cys Val Ile Asp
485 490 495

Ile Cys Met Lys Leu Glu Glu Gly Lys Tyr Leu Ile Leu Lys Asp Pro
500 505 510

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Asn Lys Gln Val Ile Arg Val Tyr Ser Leu Pro Asp Gly Thr Phe Ser
 515 520 525

Ser Asp Glu Asp Glu Glu

Glu Glu Glu Thr
545

<210> 89
<211> 670
<212> DNA
<213> *Homo sapiens*

<400> 89

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<210> 90
<211> 152
<212> PRT
<213> Homo sapien

<400> 90

Met Ala Asn Leu Glu Arg Thr Phe Ile Ala Ile Lys Pro Asp Gly Val
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Gln Arg Gly Leu Val Gly Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly
20 25 30

Phe Arg Leu Val Ala Met Lys Phe Leu Arg Ala Ser Glu Glu His Leu
35 40 45

Lys Gln His Tyr Ile Asp Leu Lys Asp Arg Pro Phe Phe Pro Gly Leu
50 55 60

Val Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val Trp Glu Gly
65 70 75 80

Leu Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro
85 90 95

Ala Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val
100 105 110

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Gly Arg Asn Ile Ile His Gly Ser Asp Ser Val Lys Ser Ala Glu Lys
 115 120 125

Glu Ile Ser Leu Trp Phe Lys Pro Glu Glu Leu Val Asp Tyr Lys Ser
 130 135 140

Cys Ala His Asp Trp Val Tyr Glu
145 150

<210> 91
<211> 1097
<212> ^DNA
<213> Homo sapiens

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Gly Lys Ala Val Val Leu Met Gly Lys Asn Thr Met Met Arg Lys Ala
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Ile Arg Gly His Leu Glu Asn Asn Pro Ala Leu Glu Lys Leu Leu Pro
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His Ile Arg Gly Asn Val Gly Phe Val Phe Thr Lys Glu Asp Leu Thr
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Glu Ile Arg Asp Met Leu Leu Ala Asn Lys Val Pro Ala Ala Ala Arg
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Gly Leu Gly Pro Glu Lys Thr Ser Phe Phe Gln Ala Leu Gly Ile Thr
 130 135 140

Thr Lys Ile Ser Arg Gly Thr Ile Glu Ile Leu Ser Asp Val Gln Leu
 145 150 155 160

Ile Lys Thr Gly Asp Lys Val Gly Ala Ser Glu Ala Thr Leu Leu Asn
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Phe Asp Asn Gly Ser Ile Tyr Asn Pro Glu Val Leu Asp Ile Thr Glu
 195 200 205

Glu Thr Leu His Ser Arg Phe Leu Glu Gly Val Arg Asn Val Ala Ser
 210 215 220

Val Cys Leu Gln Ile Gly Tyr Pro Thr Val Ala Ser Val Pro His Ser
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Ile Ile Asn Gly Tyr Lys Arg Val Leu Ala Leu Ser Val Glu Thr Asp
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Tyr Thr Phe Pro Leu Ala Glu Lys Val Lys Ala Phe Leu Ala Asp Pro
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Ser Ala Phe Val Ala Ala Ala Pro Val Ala Ala Ala Thr Thr Ala Ala
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<212> DNA

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35 40 45

Lys Gly Ser Cys Phe His Arg Ile Ile Pro Gly Phe Met Cys Gln Gly
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Gly Asp Phe Thr Arg His Asn Gly Thr Gly Gly Lys Ser Ile Tyr Gly
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Glu Lys Phe Glu Asp Glu Asn Phe Ile Leu Lys His Thr Gly Pro Gly
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Ile Leu Ser Met Ala Asn Ala Gly Pro Asn Thr Asn Gly Ser Gln Phe
100 105 110

Phe Ile Cys Thr Ala Lys Thr Glu Trp Leu Asp Gly Lys His Val Val
115 120 125

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 aagnngatca aagacatcct catcccaagta tgaccggacc ctgctggtag ttgaccctcg 420
 tcnctncgag tccaaaaagt ttgagggcct ngttcccgng gtnggtacca gaaaatctac 480
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 ttaaaaanat taaaannntg nnntnnntt nnntnnntn tnnnnnnnnn ntnnnnnnntn 600
 nnnntnnntt gggggggcn ttnccnttg ctttggggg gtttaattat tggnttgitt 660
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Ser Val Lys Ile Glu Cys Arg Ser Leu Asp Phe Gln Ala Thr Thr Met
 35 40 45

Phe Trp Tyr Arg Gln Phe Pro Lys Gln Ser Leu Met Leu Met Ala Thr
 50 55 60

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 Lys Phe Leu Ile Asn His Ala Ser Leu Thr Leu Ser Thr Leu Thr Val
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 Thr Ser Ala His Pro Glu Asp Ser Ser Phe Tyr Ile Cys Ser Ala Arg
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 Glu Ser Thr Ser Asp Pro Lys Asn Glu Gln Phe Phe Gly Pro Gly Thr
 115 120 125
 Arg Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val
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 Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala
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 Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu
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 Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp
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 Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys
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 Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg
 210 215 220
 Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp
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 Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala
 245 250 255
 Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln
 260 265 270
 Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys
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 tgctgctcac atctgtggtc cagggcaggg ccactccaga gaattacgtg taccaggac 180

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Gly Thr Gln Arg Phe Leu Glu Arg Tyr Ile Tyr Asn Arg Glu Glu Tyr
 50 55 60

Ala Arg Phe Asp Ser Asp Val Gly Glu Phe Arg Ala Val Thr Glu Leu
 65 70 75 80

Gly Arg Pro Ala Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile Leu Glu
 85 90 95

Glu Lys Arg Ala Val Pro Asp Arg Val Cys Arg His Asn Tyr Glu Leu
 100 105 110

Asp Glu Ala Val Thr Leu Gln Arg Arg Val Gln Pro Lys Val Asn Val
 115 120 125

Ser Pro Ser Lys Lys Gly Pro Leu Gln His His Asn Leu Leu Val Cys
 130 135 140

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His Val Thr Asp Phe Tyr Pro Gly Ser Ile Gln Val Arg Trp Phe Leu
 145 150 155 160

Asn Gly Gln Glu Glu Thr Ala Gly Val Val Ser Thr Asn Leu Ile Arg
 165 170 175

Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Met Thr Pro
 180 185 190

Gln Gln Gly Asp Val Tyr Ile Cys Gln Val Glu His Thr Ser Leu Asp
 195 200 205

Ser Pro Val Thr Val Glu Trp Lys Ala Gln Ser Asp Ser Ala Gln Ser
 210 215 220

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<212> PRT
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<400> 101
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20 25 30

Val Leu Glu Gly His Leu Arg Glu Arg Lys Lys Cys Leu Thr Trp Lys
35 40 45

Glu Val Trp Arg Ser Ser Phe Leu His His Ser Asn Arg Cys Ser Cys
50 55 60

Phe His Trp Pro Gly Ala Ser Leu Met Leu Leu Ala Val Leu Leu Leu
65 70 75 80

Leu Gly Cys Cys Gly Gly Gln Pro Ala Gly Ser Arg Gly Val Gly Leu
85 90 95

Val Asn Ala Ser Ala Leu Phe Leu Leu Leu Leu Asn Leu Val Leu
100 105 110

Ile Gly Arg Gln Asp Arg Leu Lys Arg Arg Glu Val Glu Arg Arg Leu
115 120 125

Arg Gly Ile Ile Asp Gln Ile Gln Asp Ala Leu Arg Asp Gly Arg Glu
130 135 140

Ile Gln Trp Pro Ser Ala Met Tyr Pro Asp Leu His Met Pro Phe Ala
145 150 155 160

Pro Ser Trp Ser Leu His Trp Ala Tyr Arg Asp Gly His Leu Val Asn
165 170 175

Leu Pro Val Ser Leu Leu Val Glu Gly Asp Ile Ile Ala Leu Arg Pro
180 185 190

Gly Gln Glu Ser Phe Ala Ser Leu Arg Gly Ile Lys Asp Asp Glu His
195 200 205

Ile Val Leu Glu Pro Gly Asp Leu Phe Pro Pro Phe Ser Pro Pro Pro
210 215 220

Ser Pro Arg Gly Glu Val Glu Arg Gly Pro Gln Ser Pro Gln Gln His
225 230 235 240

Arg Leu Phe Arg Val Leu Glu Thr Pro Val Ile Asp Asn Ile Arg Trp
245 250 255

Cys Leu Asp Met Ala Leu Ser Arg Pro Val Thr Ala Leu Asp Asn Glu
260 265 270

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Arg Phe Thr Val Gln Ser Val Met Leu His Tyr Ala Val Pro Val Val
275 280 285

Leu Ala Gly Phe Leu Ile Thr Asn Ala Leu Arg Phe Ile Phe Ser Ala
290 295 300

Pro Gly Val Thr Ser Trp Gln Tyr Thr Leu Leu Gln Leu Gln Val Asn
305 310 315 320

Gly Val Leu Pro Ile Leu Pro Leu Leu Phe Pro Val Leu Trp Val Leu
325 330 335

Ala Thr Ala Cys Gly Glu Ala Arg Val Leu Ala Gln Met Ser Lys Ala
340 345 350

Ser Pro Ser Ser Leu Leu Ala Lys Phe Ser Glu Asp Thr Leu Ser Ser
355 360 365

Tyr Thr Glu Ala Val Ser Ser Gln Glu Met Leu Arg Cys Ile Trp Gly
370 375 380

His Phe Leu Arg Val Leu Gly Gly Thr Ser Pro Thr Leu Ser His Ser
385 390 395 400

Ser Ser Leu Leu His Ser Leu Gly Ser Val Thr Val Leu Cys Cys Val
405 410 415

Asp Lys Gln Gly Ile Leu Ser Trp Pro Asn Pro Ser Pro Glu Thr Val
420 425 430

Leu Phe Phe Ser Gly Lys Val Glu Pro Pro His Ser Ser His Glu Asp
435 440 445

Leu Thr Asp Gly Leu Ser Thr Arg Ser Phe Cys His Pro Glu Pro His
450 455 460

Glu Arg Asp Ala Leu Leu Ala Gly Ser Leu Asn Asn Thr Leu His Leu
465 470 475 480

Ser Asn Glu Gln Glu Arg Gly Asp Trp Pro Gly Glu Ala Pro Lys Pro
485 490 495

Pro Glu Pro Tyr Ser His His Lys Ala His Gly Arg Ser Lys His Pro
500 505 510

Ser Gly Ser Asn Val Ser Phe Ser Arg Asp Thr Glu Gly Gly Glu Glu
515 520 525

Glu Pro Ser Lys Thr Gln Pro Gly Met Glu Ser Asp Pro Tyr Glu Ala
530 535 540

Glu Asp Phe Val Cys Asp Tyr His Leu Glu Met Leu Ser Leu Ser Gln
545 550 555 560

Asp Gln Gln Asn Pro Ser Cys Ile Gln Phe Asp Asp Ser Asn Trp Gln
565 570 575

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Leu His Leu Thr Ser Leu Lys Pro Leu Gly Leu Asn Val Leu Leu Asn
580 585 590

Leu Cys Asp Ala Ser Val Thr Glu Arg Leu Cys Arg Phe Ser Asp His
595 600 605

Leu Cys Asn Ile Ala Leu Gln Glu Ser His Ser Ala Val Leu Pro Val
610 615 620

His Val Pro Trp Gly Leu Cys Glu Leu Ala Arg Leu Ile Gly Phe Thr
625 630 635 640

Pro Gly Ala Lys Glu Leu Phe Lys Gln Glu Asn His Leu Ala Leu Tyr
645 650 655

Arg Leu Pro Ser Ala Glu Thr Met Lys Glu Thr Ser Leu Gly Arg Leu
660 665 670

Ser Cys Val Thr Lys Arg Arg Pro Pro Leu Ser His Met Ile Ser Leu
675 680 685

Phe Ile Lys Asp Thr Thr Ser Thr Glu Gln Met Leu Ser His Gly
690 695 700

Thr Ala Asp Val Val Leu Glu Ala Cys Thr Asp Phe Trp Asp Gly Ala
705 710 715 720

Asp Ile Tyr Pro Leu Ser Gly Ser Asp Arg Lys Lys Val Leu Asp Phe
725 730 735

Tyr Gln Arg Ala Cys Leu Ser Gly Tyr Cys Ser Ala Phe Ala Tyr Lys
740 745 750

Pro Met Asn Cys Ala Leu Ser Ser Gln Leu Asn Gly Lys Cys Ile Glu
755 760 765

Leu Val Gln Val Pro Gly Gln Ser Ser Ile Phe Thr Met Cys Glu Leu
770 775 780

Pro Ser Thr Ile Pro Ile Lys Gln Asn Ala Arg Arg Ser Ser Trp Ser.
785 790 795 800

Ser Asp Glu Gly Ile Gly Glu Val Leu Glu Lys Glu Asp Cys Met Gln
805 810 815

Ala Leu Ser Gly Gln Ile Phe Met Gly Met Val Ser Ser Gln Tyr Gln
820 825 830

Ala Arg Leu Asp Ile Val Arg Leu Ile Asp Gly Leu Val Asn Ala Cys
835 840 845

Ile Arg Phe Val Tyr Phe Ser Leu Glu Asp Glu Leu Lys Ser Lys Val
850 855 860

Phe Ala Glu Lys Met Gly Leu Glu Thr Gly Trp Asn Cys His Ile Ser
865 870 875 880

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Leu Thr Pro Asn Gly Asp Met Pro Gly Ser Glu Ile Pro Pro Ser Ser
885 890 895

Pro Ser His Ala Gly Ser Leu His Asp Asp Leu Asn Gln Val Ser Arg
900 905 910

Asp Asp Ala Glu Gly Leu Leu Met Glu Glu Glu Gly His Ser Asp
915 920 925

Leu Ile Ser Phe Gln Pro Thr Asp Ser Asp Ile Pro Ser Phe Leu Glu
930 935 940

Asp Ser Asn Arg Ala Lys Leu Pro Arg Gly Ile His Gln Val Arg Pro
945 950 955 960

His Leu Gln Asn Ile Asp Asn Val Pro Leu Leu Val Pro Leu Phe Thr
965 970 975

Asp Cys Thr Pro Glu Thr Met Cys Glu Met Ile Lys Ile Met Gln Glu
980 985 990

Tyr Gly Glu Val Thr Cys Cys Leu Gly Ser Ser Ala Asn Leu Arg Asn
995 1000 1005

Ser Cys Leu Phe Leu Gln Ser Asp Ile Ser Ile Ala Leu Asp Pro Leu
1010 1015 1020

Tyr Pro Ser Arg Cys Ser Trp Glu Thr Phe Gly Tyr Ala Thr Ser Ile
1025 1030 1035 1040

Ser Met Ala Gln Ala Ser Asp Gly Leu Ser Pro Leu Gln Leu Ser Gly
1045 1050 1055

Gln Leu Asn Ser Leu Pro Cys Ser Leu Thr Phe Arg Gln Glu Glu Thr
1060 1065 1070

Ile Ser Ile Ile Arg Leu Ile Glu Gln Ala Arg His Ala Thr Tyr Gly
1075 1080 1085

Ile Arg Lys Cys Phe Leu Phe Leu Leu Gln Cys Gln Leu Thr Leu Val
1090 1095 1100

Val Ile Gln Phe Leu Ser Cys Leu Val Gln Leu Pro Pro Leu Leu Ser
1105 1110 1115 1120

Thr Thr Asp Ile Leu Trp Leu Ser Cys Phe Cys Tyr Pro Leu Leu Ser
1125 1130 1135

Ile Ser Leu Leu Gly Lys Pro Pro His Ser Ser Ile Met Ser Met Ala
1140 1145 1150

Thr Gly Lys Asn Leu Gln Ser Ile Pro Lys Lys Thr Gln His Tyr Phe
1155 1160 1165

Leu Leu Cys Phe Leu Leu Lys Phe Ser Leu Thr Ile Ser Ser Cys Leu
1170 1175 1180

68/147

Ile Cys Phe Gly Phe Thr Leu Gln Ser Phe Cys Asp Ser Ser Arg Asp
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Arg Asn Leu Thr Asn Cys Ser Ser Val Met Leu Pro Ser Asn Asp Asp
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Arg Ala Pro Ala Trp Phe Glu Asp Phe Ala Asn Gly Leu Leu Ser Ala
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Gln Lys Leu Thr Ala Ala Leu Ile Val Leu His Thr Val Phe Ile Ser
 1235 1240 1245

Ile Thr His Val His Arg Thr Lys Pro Leu Trp Arg Lys Ser Pro Leu
 1250 1255 1260

Thr Asn Leu Trp Trp Ala Val Thr Val Pro Val Val Leu Leu Gly Gln
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Val Val Gln Thr Ala Val Asp Leu Gln Leu Trp Thr His Arg Asp Ser
 1285 1290 1295

His Val His Phe Gly Leu Glu Asp Val Pro Leu Leu Thr Trp Leu Leu
 1300 1305 1310

Gly Cys Leu Ser Leu Val Leu Val Val Val Thr Asn Glu Ile Val Lys
 1315 1320 1325

Leu His Glu Ile Arg Val Arg Val Arg Tyr Gln Lys Arg Gln Lys Leu
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Gln Phe Glu Thr Lys Leu Gly Met Asn Ser Pro Phe
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<210> 102

<211> 2030

<212> DNA

<213> Homo sapiens

<400> 102

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<211> 318

<212> PRT

<213> Homo sapiens

<400> 103

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													20	25	30

Asp	Asp	Leu	Val	Thr	Ile	Ser	Glu	Leu	Gly	Arg	Gly	Ala	Tyr	Gly	Val
												35	40	45	

Val	Glu	Lys	Val	Arg	His	Ala	Gln	Ser	Gly	Thr	Ile	Met	Ala	Val	Lys
												50	55	60	

Arg	Ile	Arg	Ala	Thr	Val	Asn	Ser	Gln	Glu	Gln	Lys	Arg	Leu	Leu	Met
65												65	70	75	80

Asp	Leu	Asp	Ile	Asn	Met	Arg	Thr	Val	Asp	Cys	Phe	Tyr	Thr	Val	Thr
													85	90	95

Phe	Tyr	Gly	Ala	Leu	Phe	Arg	Glu	Gly	Asp	Val	Trp	Ile	Cys	Met	Glu
												100	105	110	

Leu	Met	Asp	Thr	Ser	Leu	Asp	Lys	Phe	Tyr	Arg	Lys	Val	Leu	Asp	Lys
												115	120	125	

Asn	Met	Thr	Ile	Pro	Glu	Asp	Ile	Leu	Gly	Glu	Ile	Ala	Val	Ser	Ile
												130	135	140	

Val	Arg	Ala	Leu	Glu	His	Leu	His	Ser	Lys	Leu	Ser	Val	Ile	His	Arg
145												145	150	155	160

Asp	Val	Lys	Pro	Ser	Asn	Val	Leu	Ile	Asn	Lys	Glu	Gly	His	Val	Lys
												165	170	175	

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Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val Ala Lys
 180 185 190

Thr Met Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn
 195 200 205

Pro Glu Leu Asn Gln Lys Gly Tyr Asn Val Lys Ser Asp Val Trp Ser
 210 215 220

Leu Gly Ile Thr Met Ile Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu
 225 230 235 240

Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val Glu Glu Pro
 245 250 255

Ser Pro Gln Leu Pro Ala Asp Arg Phe Ser Pro Glu Phe Val Asp Phe
 260 265 270

Thr Ala Gln Cys Leu Arg Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu
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Glu Leu Met Glu His Pro Phe Phe Thr Leu His Lys Thr Lys Lys Thr
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Asp Ile Ala Ala Phe Val Lys Lys Ile Leu Gly Glu Asp Ser
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<210> 104

<211> 1648

<212> DNA

<213> Homo sapiens

<400> 104

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 gccgcctgcg accccgcgcca cggccgtatcc ctgacgggtgg ccaccgtgtt cccggggcc 960
 atgtccatga aggaggtggc ctagccatcc agagcaagaa cagcagctac 1020
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 ctcaagatgt cctccacccat ctagggaaac agcacggcca tccaggagct gttcaagcgc 1140
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 gagtaccagc agtaccagga cggccacggcc gaggaaaggagg gcgagatgtt cgaagacgac 1320
 gagggaggat cggaggccca gggccccaa tggaaactgtt cgcagctgga gtgagaggca 1380
 ggtggcgccc gggggccgaag ccagcagtgt ctaaaccctt ggagccatct tgctgccac 1440

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accctgctt cccatcgcc ctagggctcc cttgccgcc tcctgcagta tttatggcct 1500
 cgtcctcccc cacctaggcc acgtgtgagc tgctcctgtc tctgtcttat tgcagctcca 1560
 ggcctgacgt ttacggtt tgttttac tggtttgtt gtatatttc ggggataactt 1620
 aataaatcta ttgctgtcag ataccctt 1648

<210> 105
 <211> 450
 <212> PRT
 <213> Homo sapiens

<400> 105
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 1 5 10 15
 Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
 20 25 30
 Ser Gly Asn Tyr Val Gly Asp Ser Asp Leu Gln Leu Glu Arg Ile Ser
 35 40 45
 Val Tyr Tyr Asn Glu Ala Ser Ser His Lys Tyr Val Pro Arg Ala Ile
 50 55 60
 Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Ala
 65 70 75 80
 Phe Gly His Leu Phe Arg Pro Asp Asn Phe Ile Phe Gly Gln Ser Gly
 85 90 95
 Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
 100 105 110
 Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Cys Glu Asn Cys Asp
 115 120 125
 Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Thr Gly
 130 135 140
 Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Val Arg Glu Glu Tyr Pro
 145 150 155 160
 Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
 165 170 175
 Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Ile His Gln Leu
 180 185 190
 Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
 195 200 205
 Asp Ile Cys Phe Arg Thr Leu Lys Leu Ala Thr Pro Thr Tyr Gly Asp
 210 215 220
 Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Ser Leu
 225 230 235 240

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Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
 245 250 255

 Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
 260 265 270

 Leu Thr Arg Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
 275 280 285

 Leu Thr Gln Gln Met Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
 290 295 300

 Pro Arg His Gly Arg Tyr Leu Thr Val Ala Thr Val Phe Arg Gly Arg
 305 310 315 320

 Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Ala Ile Gln Ser Lys
 325 330 335

 Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Val Ala
 340 345 350

 Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ser Ser Thr Phe Ile
 355 360 365

 Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
 370 375 380

 Phe Thr Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Tyr Thr Gly
 385 390 395 400

 Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
 405 410 415

 Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Ala Glu Glu
 420 425 430

 Glu Gly Glu Met Tyr Glu Asp Asp Glu Glu Glu Ser Glu Ala Gln Gly
 435 440 445

 Pro Lys
 450

<210> 106
 <211> 1633
 <212> DNA
 <213> Homo sapiens

<400> 106
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 catttaaaaag gtagaacagg atcgacaaac aaggatttat gtcagatct ctcagcctct 180
 gtgttaccga gggcatttct aacagtcttc ttactacggc ctccggcgac cgccgcgtcg 240
 ccccgccgct cctgctgcag ccccaggggcc cctcgccgccc gccaccatgg acgccatcaa 300
 gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag ctgagcaggc 360
 ggaggccgac aagaaggcgg cggaaagacag gagcaagcag ctgaaagatg agctgggtgc 420
 actgaaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg aggctctcaa 480
 agatgccccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg aagccgacgt 540

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agcttctctg aacagacgc a tccagctgg tgaggaagag ttggatcg cccaggagc 600
tctggcaaca gcttgccaga agctggagga agctgagaag gcacgcgatg agagtggag 660
aggcatgaaa gtcattgaga gtcgagccc aaaagatgaa gaaaaaatgg aaattcagg 720
gatccaactg aaagaggcaa agcacattgc tgaagatgcc gaccgcaat atgaagagg 780
ggcccgttaag ctggcatca ttgagagcga cctggAACGT gcagaggagc gggctggact 840
ctcagaaggc caagtccgac agctggaga acaattaaga ataatggatc agaccttggaa 900
agcattaatg gctgcagagg ataagtactc gcagaaggaa gacagatatg aggaagagat 960
caagggtccct tccgacaagc tgaaggagc tgagactcgq gctgagttt cgagagggtc 1020
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aaaacccctt tagctgcgac cacattctt cattttgtt tgggggttt tggttttaaa 1200
cacctgctta ccccttaaat gcaatttt tacttttacc actgtcacag aaacatccac 1260
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caaagtgcacat atgatagagt caacaaggaa ggtaatgtt gggaaacacaa tcaggtgtgg 1500
atgggtgcta ctttgaaccaa aaggcccccc tgggtcttt tggtcaacat tgtacaatgt 1560
agaactctgt ccaacactaa ttatgttctt cttgagttt actacaagat gagactatgg 1620
atccccggatc cct 1633

<210> 107

<211> 284

<212> PRT

<213> Homo sapiens

<400> 107

Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
 1 5 10 15

Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
20 25 30

Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
35 40 45

Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
50 55 60

Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
65 70 75 80

Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
85 90 95

Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
 100 105 110

Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
115 120 125

Val	Ile	Glu	Ser	Arg	Ala	Gln	Lys	Asp	Glu	Glu	Lys	Met	Glu	Ile	Gln
130						135						140			

Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
145 150 155 160

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Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
 165 170 175

Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Gln Val Arg Gln
 180 185 190

Leu Glu Glu Gln Leu Arg Ile Met Asp Gln Thr Leu Lys Ala Leu Met
 195 200 205

Ala Ala Glu Asp Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu
 210 215 220

Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
 225 230 235 240

Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
 245 250 255

Glu Glu Lys Val Ala His Ala Lys Glu Glu Asn Leu Ser Met His Gln
 260 265 270

Met Leu Asp Gln Thr Leu Leu Glu Leu Asn Asn Met
 275 280

<210> 108

<211> 1835

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (44)..(44)

<223> n is a, c, g, or t

<220>

<221> misc_feature

<222> (71)..(71)

<223> n is a, c, g, or t

<400> 108

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 acaggaaaca nctatgacct tgattacgccc aagctcgaaa ttaaccctca ctaaaggaa 120
 caaaagctgg agctcgccgc cctgcaggc gacactagt gatccaaaga attcggcacg 180
 aggcgacggg cggagcggag cggccgcgc cggggccgccc gcccggggga tcggctgcct 240
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 cataggagggc ggccatggcg accccccggca acctagggtc ctccgtcctg gcgagcaaga 360
 ccaagaccaa gaagaagcac ttctgtcgcc agaaaagt gatgt gctgttcgg gccagcgacc 420
 cgctgctca gctcctcatg tggggggtaa accactcgat caatgaactg agccatgttc 480
 aaatccctgt tatgttgatg ccagatgact tcaaaggcta ttcaaaaata aaggtggaca 540
 atcaccttt taacaaagaa aacatgccc gccatttcaa gtttaaggaa tactgcccga 600
 tggcttccg taactgcggg aagagggttg gaattgtatgt tcaagatttc cagaattccc 660
 tgaccaggag cgcacccctc cccaaacgact cccaggcccg cagtggagct cgtttcaca 720
 cttcctacga caaaagatac atgatcaaga ctattaccag tgaagacgtg gccgaaatgc 780
 acaacatcct gaagaaatac caccagtaca tagtggatg tcatggatc acccttctc 840
 cccacttgtt gggcatgtac cggcttaatg ttgtatggatg taaaatataat gtgatagtt 900
 caagaaatgt attcagccac cgtttgtctg tggataggaa atacgactta aagggctcta 960
 cagtggctag agaagctgt gacaaagaaa agccaaaga actgccaact ctgaaagata 1020

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atgatttcat	taatgagggc	caaaaagattt	atattgtatga	caacagcaag	aaggcttcc	1080
tggaaaaact	aaaaaaaggat	gttgagttc	tggcccaact	gaagctcatg	gactacagtc	1140
tgctgggggg	aattcatgtat	gtggagagag	ccgaacagga	ggaagtggag	tgtgaggaga	1200
acgatgggg	ggaggagggc	gagagcgtat	gcacccaccc	ggtggaaacc	cccccaagata	1260
gccccgggaa	tacactgaac	agctaccac	ccctggotcc	cggggagttc	gagccgaaca	1320
tcgacgtcta	tggaattaag	tgccatgaaa	actcgcttag	gaaggaggtg	tacttcatgg	1380
caattattga	catccttact	cattatgtat	caaaaaagaa	agctgcccatt	gctgcaaaaa	1440
ctgttaaaca	tggcgctqgc	gcggagatct	ccacccgtgaa	cccagaacag	tattcaaagc	1500
gctttttgg	cattttttggc	cacatcttga	cgtaacctcc	tgcgcayctc	ggacagcatg	1560
aacattggat	ggacagaggt	ggcttcggtg	tagaaaaat	gaaaacccaa	ctcagtgaa	1620
tactcatctt	gcaggaagca	aaccccttgc	tttacatctt	caggccaaga	tgactgattt	1680
gggggctact	cgttttacag	ctacctgttt	ttcccagcat	cgttctagct	atttctgact	1740
tttgttatat	gtgtgtgtgt	gtgtgttggg	gggggggtgag	tgtgtgcccg	cgtgtgcatt	1800
taaagcataa	attaatttaaa	cagccacttc	ggta			1835

<210> 109

<211> 406

<212> PBT

<213> Homo sapiens

<400> 109

Met Ala Thr Pro Gly Asn Leu Gly Ser Ser Val Leu Ala Ser Lys Thr
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Lys Thr Lys Lys His Phe Val Ala Gln Lys Val Lys Leu Phe Arg
20 25 30

Ala Ser Asp Pro Leu Leu Ser Val Leu Met Trp Gly Val Asn His Ser
35 40 45

Ile Asn Glu Leu Ser His Val Gln Ile Pro Val Met Leu Met Pro Asp
50 55 60

Asp Phe Lys Ala Tyr Ser Lys Ile Lys Val Asp Asn His Leu Phe Asn
65 70 75 80

Lys Glu Asn Met Pro Ser His Phe Lys Phe Lys Glu Tyr Cys Pro Met
85 90 95

Val Phe Arg Asn Cys Gly Lys Arg Phe Gly Ile Asp Val Gln Asp Phe
100 105 110

Gln Asn Ser Leu Thr Arg Ser Ala Pro Leu Pro Asn Asp Ser Gln Ala
115 120 125

Arg Ser Gly Ala Arg Phe His Thr Ser Tyr Asp Lys Arg Tyr Met Ile
130 135 140

Lys	Thr	Ile	Thr	Ser	Glu	Asp	Val	Ala	Glu	Met	His	Asn	Ile	Leu	Lys
145				150					155					160	

Lys Tyr His Gln Tyr Ile Val Glu Cys His Gly Ile Thr Leu Leu Pro
 165 170 175

His Leu Leu Gly Met Tyr Arg Leu Asn Val Asp Gly Val Glu Ile Tyr
180 185 190

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Lys Tyr Asp Leu Lys Gly Ser Thr Val Ala Arg Glu Ala Ser Asp Lys
210 215 220

Glu Lys Ala Lys Glu Leu Pro Thr Leu Lys Asp Asn Asp Phe Ile Asn
225 230 235 240

Glu Gly Gln Lys Ile Tyr Ile Asp Asp Asn Ser Lys Lys Val Phe Leu
245 250 255

Glu Lys Leu Lys Lys Asp Val Glu Phe Leu Ala Gln Leu Lys Leu Met
260 265 270

Asp Tyr Ser Leu Leu Val Gly Ile His Asp Val Glu Arg Ala Glu Gln
 275 280 285

Glu Glu Val Glu Cys Glu Glu Asn Asp Gly Glu Glu Glu Gly Glu Ser
290 295 300

Asp Gly Thr His Pro Val Gly Thr Pro Pro Asp Ser Pro Gly Asn Thr
305 310 315 320

Leu Asn Ser Ser Pro Pro Leu Ala Pro Gly Glu Phe Glu Pro Asn Ile
325 330 335

Asp Val Tyr Gly Ile Lys Cys His Glu Asn Ser Pro Arg Lys Glu Val
 340 345 350

Tyr Phe Met Ala Ile Ile Asp Ile Leu Thr His Tyr Asp Ala Lys Lys
355 360 365

Lys Ala Ala His Ala Ala Lys Thr Val Lys His Gly Ala Gly Ala Glu
370 375 380

Ile Ser Thr Val Asn Pro Glu Gln Tyr Ser Lys Arg Phe Leu Asp Phe
385 390 395 400

Ile Gly His Ile Leu Thr
405

<210> 110

2572

<212> DNA

<213> Homo sapiens

<400> 110

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gggtccttct	ggctctgaag	gcaatgatct	ggggcatgga	acctgttagtt	agagagctgg	180
gaaatggca	gatgtgggc	ccagggcacc	cagaattgca	ggcttaggag	ctaacaagcaa	240
ccaggattct	gtagtcttagc	aatcttgctt	tacaggtgag	gaaactggc	ctagaaaaggc	300
gaagtgattt	ttttgcctct	ctcagcttta	ttcctctttt	cctctgaact	gtagagtcta	360
aagattcagc	acaaagcagt	tttgtgttagt	ggatacacataa	gctttttgt	tgttatTTT	420
ctgaattatt	tttgtgactt	tcaaagtttt	ttttacataa	acagtaaaatg	ctcggtataa	480
aaatttccat	taatacagga	agtaaaaaaaaa	gtaaaaaaaaa	gcaaaattgt	gttatcctcc	540

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cacccttacc cccttaggtcc ccagagggtgt ctctgttaac agttcagcgt gtatccatcc 600
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 acattattca agcataggct ttagactcag acatatctac atctaattccc agcttatagc 720
 taattatttg agtgaccttg gccaagttgt tcataccagg ttatgtctaa tctccccatg 780
 tgtaaaatga aaataataat agtatctacc tggcctggcg tggcgctta tgcctataat 840
 cccagccctt tggaaagaccg aggctagttg atccctttag ctcaggagtt caagaccaac 900
 ctgggcaatt tagcaagacc tcatactctac tggaaaaacaa aaaacaaaaa aactccccca 960
 aaatttagcca agtgtgctgg tggcacctg tagtcccagc tactcggaa gctgagggtgg 1020
 gagaatcgt tgagccagga aagacgaggc tgcagtgagc tgtgattgca ccactgcact 1080
 gcaaccttag caacagagcg ataccttgg tctgttaaaa caaacaaca aacaaaatag 1140
 tatctacccat atagatcat ggtgaagatt taatgagatt ttatgtaaat agcacttaac 1200
 agttccttgtt actgatagta gtaagcacta cacacacaca cacacacaca cacacacaca 1260
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 tgtgagttgg gaggggtgtgg ggcagtgtgg gttggctgga ccagctgtt cttcagagct 1560
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 ctgtcctgtt acccttagatt tggcagctt agttggaaat gggggaggt acaaccaacc 2520
 atccatccac cttttataa ggcattaatg aggaccacca tagcaaagta aa 2572

<210> 111

<211> 197

<212> PRT

<213> Homo sapiens

<400> 111

Met	Ala	Pro	Lys	Lys	Pro	Glu	Pro	Lys	Lys	Glu	Ala	Ala	Lys	Pro	Ala
1														15	

Pro	Ala	Pro	Glu													
														20	25	30

Ala	Pro	Lys	Glu	Pro	Ala	Phe	Asp	Pro	Lys	Ser	Val	Lys	Ile	Asp	Phe	
														35	40	45

Thr	Ala	Asp	Gln	Ile	Glu	Glu	Phe	Lys	Glu	Ala	Phe	Ser	Leu	Phe	Asp	
														50	55	60

Arg	Thr	Pro	Thr	Gly	Glu	Met	Lys	Ile	Thr	Tyr	Gly	Gln	Cys	Gly	Asp		
														65	70	75	80

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Val Leu Arg Ala Leu Gly Gln Asn Pro Thr Asn Ala Glu Val Leu Arg
 85 90 95

Val Leu Gly Lys Pro Lys Pro Glu Glu Met Asn Val Lys Met Leu Asp
 100 105 110

Phe Glu Thr Phe Leu Pro Ile Leu Gln His Ile Ser Arg Asn Lys Glu
 115 120 125

Gln Gly Thr Tyr Glu Asp Phe Val Glu Gly Leu Arg Val Phe Asp Lys
 130 135 140

Glu Ser Asn Gly Thr Val Met Gly Ala Glu Leu Arg His Val Leu Ala
 145 150 155 160

Thr Leu Gly Glu Lys Met Thr Glu Ala Glu Val Glu Gln Leu Leu Ala
 165 170 175

Gly Gln Glu Asp Ala Asn Gly Cys Ile Asn Tyr Glu Ala Phe Val Lys
 180 185 190

His Ile Met Ser Gly
 195

<210> 112

<211> 1011

<212> DNA

<213> Homo sapiens

<400> 112

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 ctgaccgaca actacatgtc cctggtcatt gatgtatgaga ccaaggaggc tgccatttgt 120
 gatccgtgtc agccccagaa ggtcggtggac gcccggagaa agcacgggggt gaaactgacc 180
 acagtgccta ccaccacca ccactgggac catgctggcg ggaatgagaa actggtaaag 240
 ctggagtcgg gactgaaggt gtacgggggt gacgaccgta tcggggccct gactcacaag 300
 atcactcacc tgtccacact gcaggtgggg tctctgaacg tcaagtgcct ggccgaccccg 360
 tgccacaccc caggacacat ttgttacttc gtgagcaagc ccggagggtc ggagccccct 420
 gccgtgttca caggtgacac cttgtttgtc gctggctgcg ggaaggctca tgaaggggact 480
 gcgatgaga tggatgaaaagc tctgctggag gtcttggggcc ggctcccccc ggacacacaaga 540
 gtctactgtc gccacgagta caccatcaac aacctcaagt ttgcacgcca cgtggagccc 600
 ggcaatgccc ccatccggga gaagctggcc tggccaaagg agaagttacag catcggggag 660
 cccacagtgc catccacccct ggcagaggag tttacctaca accccttcat gagagtggagg 720
 gagaagacgg tgcagcagca cgccaggtgag acggaccggc tgaccaccat gcccggccgtg 780
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 gatttggggta tttaggtactt tttaggtactt ggctttcctg ctggccgtg cggaaatc 900
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 tatttataag agaagttaa caagtatttta ttccctataaa aaaaaaaaaa a 1011

<210> 113

<211> 260

<212> PRT

<213> Homo sapiens

<400> 113

Met Lys Val Glu Val Leu Pro Ala Leu Thr Asp Asn Tyr Met Tyr Leu
 1 5 10 15

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Val Ile Asp Asp Glu Thr Lys Glu Ala Ala Ile Val Asp Pro Val Gln
 20 25 30

Pro Gln Lys Val Val Asp Ala Ala Arg Lys His Gly Val Lys Leu Thr
 35 40 45

Thr Val Leu Thr Thr His His Trp Asp His Ala Gly Gly Asn Glu
 50 55 60

Lys Leu Val Lys Leu Glu Ser Gly Leu Lys Val Tyr Gly Gly Asp Asp
 65 70 75 80

Arg Ile Gly Ala Leu Thr His Lys Ile Thr His Leu Ser Thr Leu Gln
 85 90 95

Val Gly Ser Leu Asn Val Lys Cys Leu Ala Thr Pro Cys His Thr Ser
 100 105 110

Gly His Ile Cys Tyr Phe Val Ser Lys Pro Gly Gly Ser Glu Pro Pro
 115 120 125

Ala Val Phe Thr Gly Asp Thr Leu Phe Val Ala Gly Cys Gly Lys Phe
 130 135 140

Tyr Glu Gly Thr Ala Asp Glu Met Cys Lys Ala Leu Leu Glu Val Leu
 145 150 155 160

Gly Arg Leu Pro Pro Asp Thr Arg Val Tyr Cys Gly His Glu Tyr Thr
 165 170 175

Ile Asn Asn Leu Lys Phe Ala Arg His Val Glu Pro Gly Asn Ala Ala
 180 185 190

Ile Arg Glu Lys Leu Ala Trp Ala Lys Glu Lys Tyr Ser Ile Gly Glu
 195 200 205

Pro Thr Val Pro Ser Thr Leu Ala Glu Glu Phe Thr Tyr Asn Pro Phe
 210 215 220

Met Arg Val Arg Glu Lys Thr Val Gln Gln His Ala Gly Glu Thr Asp
 225 230 235 240

Pro Val Thr Thr Met Arg Ala Val Arg Arg Glu Lys Asp Gln Phe Lys
 245 250 255

Met Pro Arg Asp
 260

<210> 114
 <211> 2233
 <212> DNA
 <213> Homo sapiens

<400> 114
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 gatatgcgtt cgtggttgcc ttggtcctcc tgaacgtcgc agcggcgaaa gccgtcccc 120

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35 40 45

Arg Pro Gly Gly Ser Thr Lys Ser His Pro Glu Pro Gln Thr Pro Lys
50 55 60

Asp Ser Pro Ser Lys Ser Ser Ala Glu Ala Gln Thr Pro Glu Asp Thr
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Pro Asn Lys Ser Gly Gly Glu Ala Lys Thr Leu Lys Asp Ser Ser Asn
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Lys Ser Gly Ala Glu Ala Gln Thr Pro Lys Gly Ser Thr Ser Lys Ser
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Gly Ser Glu Ala Gln Thr Thr Lys Asp Ser Thr Ser Lys Ser His Pro
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Glu Leu Gln Thr Pro Lys Asp Ser Thr Gly Lys Ser Gly Ala Glu Ala
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Gln Thr Pro Glu Asp Ser Pro Asn Arg Ser Gly Ala Glu Pro Lys Thr
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Gln Lys Asp Ser Pro Ser Lys Ser Gly Ser Glu Ala Gln Thr Thr Lys
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Asp Val Pro Asn Lys Ser Gly Ala Asp Gly Gln Thr Pro Lys Asp Gly
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Ser Ser Lys Ser Gly Ala Glu Asp Gln Thr Pro Lys Asp Val Pro Asn
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Glu Glu Gln Thr Ser Lys Asp Ser Pro Asn Lys Val Val Pro Glu Gln
245 250 255

Pro Ser Arg Lys Asp His Ser Lys Pro Ile Ser Asn Pro Ser Asp Asn
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Val Gly Pro Lys Glu Ala Glu Asp Asp Asp Thr Gly Pro Glu Glu Gly
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Ser Pro Pro Lys Glu Glu Lys Glu Lys Met Ser Gly Ser Ala Ser Ser
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Glu Asn Arg Glu Gly Thr Leu Ser Asp Ser Thr Gly Ser Glu Lys Asp
355 360 365

Asp Leu Tyr Pro Asn Gly Ser Gly Asn Gly Ser Ala Glu Ser Ser His
370 375 380

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Phe Phe Ala Tyr Leu Val Thr Ala Ala Ile Leu Val Ala Val Leu Tyr
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Val His Pro Asp Thr Gly Ile Ser Ser Lys Ala Met Gly Ile Met Asn
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Ser Phe Val Asn Asp Ile Phe Glu Arg Ile Ala Gly Glu Ala Ser Arg
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Leu Ala His Tyr Asn Lys Arg Ser Thr Ile Thr Ser Arg Glu Ile Gln
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aataaaagag aaacccaaag aagaaaagca taaagaagaa aagcacaaag aaaaaaaca 660
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Ile Ser Pro Thr Lys Phe Pro Gly Leu Tyr Arg Thr Gly Glu Pro Ser
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Pro Pro His Asp Ile Leu His Glu Pro Pro Asp Val Val Ser Asp Asp
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Glu Lys Asp His Gly Lys Lys Lys Gly Lys Phe Lys Lys Lys Glu Lys
65 70 75 80

Arg Thr Glu Gly Tyr Ala Ala Phe Gln Glu Asp Ser Ser Gly Asp Glu
85 90 95

Ala Glu Ser Pro Ser Lys Met Lys Arg Ser Lys Gly Ile His Val Phe
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Lys Lys Pro Ser Phe Ser Lys Lys Lys Glu Lys Asp Phe Lys Ile Lys
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Glu Lys Pro Lys Glu Glu Lys His Lys Glu Glu Lys His Lys Glu Glu
 130 135 140

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Lys His Lys Glu Lys Lys Ser Lys Asp Leu Thr Ala Ala Asp Val Val
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Lys Gln Trp Lys Glu Lys Lys Lys Lys Pro Ile Gln Glu Pro
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Glu Val Pro Gln Ile Asp Val Pro Asn Leu Lys Pro Ile Phe Gly Ile
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Pro Leu Ala Asp Ala Val Glu Arg Thr Met Met Tyr Asp Gly Ile Arg
195 200 205

Leu Pro Ala Val Phe Arg Glu Cys Ile Asp Tyr Val Glu Lys Tyr Gly
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Met Lys Cys Glu Gly Ile Tyr Arg Val Ser Gly Ile Lys Ser Lys Val
225 230 235 240

Asp Glu Leu Lys Ala Ala Tyr Asp Arg Glu Glu Ser Thr Asn Leu Glu
245 250 255

Asp Tyr Glu Pro Asn Thr Val Ala Ser Leu Leu Lys Gln Tyr Leu Arg
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Asp Leu Pro Glu Asn Leu Leu Thr Lys Glu Leu Met Pro Arg Phe Glu
275 280 285

Glu Ala Cys Gly Arg Thr Thr Glu Thr Glu Lys Val Gln Glu Phe Gln
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Arg Leu Leu Lys Glu Leu Pro Glu Cys Asn Tyr Leu Leu Ile Ser Trp
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Leu Ile Val His Met Asp His Val Ile Ala Lys Glu Leu Glu Thr Lys
325 330 335

Met Asn Ile Gln Asn Ile Ser Ile Val Leu Ser Pro Thr Val Gln Ile
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Ser Asn Arg Val Leu Tyr Val Phe Phe Thr His Val Gln Glu Leu Phe
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Gly Asn Val Val Leu Lys Gln Val Met Lys Pro Leu Arg Trp Ser Asn
370 375 380

Met Ala Thr Met Pro Thr Leu Pro Glu Thr Gln Ala Gly Ile Lys Glu
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Gln Gly Gly Ile Lys Asp Leu Ser Lys Glu Glu Arg Leu Trp Glu Val
420 425 430

Gln Arg Ile Leu Thr Ala Leu Lys Arg Lys Leu Arg Glu Ala Lys Arg
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 465 470 475 480

Ile Leu Leu Ala Gln Glu Asn Glu Ile Leu Thr Glu Gln Glu Glu Leu
 485 490 495

Leu Ala Met Glu Gln Phe Leu Arg Arg Gln Ile Ala Ser Glu Lys Glu
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Glu Ile Glu Arg Leu Arg Ala Glu Ile Ala Glu Ile Gln Ser Arg Gln
 515 520 525

Gln His Gly Arg Ser Glu Thr Glu Glu Tyr Ser Ser Glu Ser Glu Ser
 530 535 540

Glu Ser Glu Asp Glu Glu Glu Leu Gln Ile Ile Leu Glu Asp Leu Gln
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Arg Gln Asn Glu Glu Leu Glu Ile Lys Asn Asn His Leu Asn Gln Ala
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Ile His Glu Glu Arg Glu Ala Ile Ile Glu Leu Arg Val Gln Leu Arg
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Glu Glu Pro Glu Trp Arg Gly Gly Ala Val Gln Pro Pro Arg Asp Gly
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<222> (709)..(712)
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caactgatgag ntctgggggn tctgcacaca cccctcccag aaccgnttcc tcacctgogg 180
ccacgaccgg nagttctgcc ttggggatgg ggagagccat gcactggcct ggagcatcga 240
cctcaaggag actggctctgtgactt ccaccccgagt ggggcagttg tggccgnagg 300
actgaacacg gggaggttgttggttttgn cacagagacc agagagatcg tgtctgatgt 360
cattgatggc aatnagcagc tctcagttgtt ccggtagcagn ccagatgggt tggcctggc 420
ccaattgggtt cccccatnaca acntnatntt caatctttt gnngtttcca ggggatggtg 480
cccaattcca gnccnttttgc ggcncnttgc ntttgggtca acncccgant tcaaccactc 540
aatnttggag tagttcaan nnttngnntt accagttgnn ntnttccaan nnnnnnnnnnn 600
nntntnnntt nnttnttctt ttncntrann cnnnnnnnnnnn nnncnnntctn ctnnttnttc 660
aanccnnntn nnnnnncnnn cnnnnnncntn tnncntncntn nnncnnntnn nnctnnntnn 720
cnnnnnnctnn nnntnnncnn nnnnnnn 746

<210> 121
<211> 1211
<212> DNA
<213> Homo sapiens

<400> 121
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gcagaaggac tacggggcccc ggcgaccggc gggcgggggc ttccggcgcc ctgccttgc 120
ggcacggtag ttccggccggg tctggcttcc gcctgcccgg cggcccccggc ccgcaggccg 180
gactacactt cccgtcgcc cgcctgcct cccgatggcc ccttggcgcc agacgttgc 240
aaggcagatgt tctccaagat ggccgcttgg ggaaggaggc gtcttggccc gggcagcgt 300
ggcggcagcg cccgagagag ggtgagcttg tcggccacag actgctacat tgtgcatgag 360
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 atcaccgtgg gcaactgcct gcacaagacg gccgtgctgg cgggcaccgc ctgcctcttc 540
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 caagtggagt acgacgccta taaaactgtcg cgcctgcctc tgcacacact cacctcctcc 720
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 gcactggccg ccctgggtta ctgtgttaaag aagatttacg aactctatgc cgtatgatt 840
 cagtagaaca gggagcgaag caaaaaccacc cggcccacaa gagacaacag agtattcaga 900
 tcgcccacact ctgtgaggca gcagagcctg ggcaggtgtt tggcttagta tttgttattt 960
 ttaaaaaata acagatcacg ggtgtaccca gggttttca gctcattaca ctaagatgtg 1020
 gatttccata acccaagagg ggggtctgag gctgtggaag tccgactggg cagtggaatg 1080
 ctgatggagg cagacgctgc cgaggggggtg tggacgtgct ttgggggagg tcttaagt 1140
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 atttcaactc c 1211

<210> 122

<211> 192

<212> PRT

<213> Homo sapiens

<400> 122

Met	Ala	Ala	Trp	Gly	Arg	Arg	Arg	Leu	Gly	Pro	Gly	Ser	Ser	Gly	Gly
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Ser	Ala	Arg	Glu	Arg	Val	Ser	Leu	Ser	Ala	Thr	Asp	Cys	Tyr	Ile	Val
			20					25						30	

His	Glu	Ile	Tyr	Asn	Gly	Glu	Asn	Ala	Gln	Asp	Gln	Phe	Glu	Tyr	Glu
				35				40						45	

Leu	Glu	Gln	Ala	Leu	Glu	Ala	Gln	Tyr	Lys	Tyr	Ile	Val	Ile	Glu	Pro
			50				55				60				

Thr	Arg	Ile	Gly	Asp	Glu	Thr	Ala	Arg	Trp	Ile	Thr	Val	Gly	Asn	Cys
				65			70			75				80	

Leu	His	Lys	Thr	Ala	Val	Leu	Ala	Gly	Thr	Ala	Cys	Leu	Phe	Thr	Pro
				85					90					95	

Leu	Ala	Leu	Pro	Leu	Asp	Tyr	Ser	His	Tyr	Ile	Ser	Leu	Pro	Ala	Gly
				100				105					110		

Val	Leu	Ser	Leu	Ala	Cys	Cys	Thr	Leu	Tyr	Gly	Ile	Ser	Trp	Gln	Phe
				115				120			125				

Asp	Pro	Cys	Cys	Lys	Tyr	Gln	Val	Glu	Tyr	Asp	Ala	Tyr	Lys	Leu	Ser
				130			135			140					

Arg	Leu	Pro	Leu	His	Thr	Leu	Thr	Ser	Ser	Thr	Pro	Val	Val	Leu	Val
				145			150			155			160		

Arg	Lys	Asp	Asp	Leu	His	Arg	Lys	Arg	Leu	His	Asn	Thr	Ile	Ala	Leu
				165					170				175		

Ala	Ala	Leu	Val	Tyr	Cys	Val	Lys	Lys	Ile	Tyr	Glu	Leu	Tyr	Ala	Val
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<210> 123
<211> 1568
<212> DNA
<213> Homo sapiens

<400> 123

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cgccctgagcg agagcagagg aggaggaggc atgagtgagg cgggcgaggc caccaccacc 240
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cacgtcgcaag gaaaccccccgg tggggacgcg gcccctgcag ccacgggcac cgcggccggc 420
gcctcttttag cgcgcgcgc cggcagcga gacgcggaga aaaaagttct cgccaccaa 480
gtccttggca ctgtcaaatg gttcaacgtc agaaaatggat atggatttat aaatcgaaat 540
gacaccaaag aagatgtatt tgtacatcg actgcctatca agaagaataa cccacggaaa 600
tatctgcgca gtgttaggaga tggagaaact gtagagtttgc atgtggttga aggagagaag 660
gggtcagaag ctgcataatgt gactggcccg gatggagttc ctgtggaaagg gagtcgttac 720
gctgcagatc ggcgcgcgtta cagacgtggc tactatggaa ggcgcgcgtgg ccctcccccgg 780
aattacgctg gggaggagga ggaggaaggg agcggcagca gtgaaggatt tgaccccccct 840
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cagtaccggc agcggcggtt cccgccttac cacgtgggac agaccttgc cgctcgctca 960
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catccaagca ataaaatgggaa agactaacca agatttggac attggaatgt ttactgttat 1500
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<210> 124
<211> 412
<212> PRT
<213> Homo sapiens

<400> 124

Glu	Phe	Gly	Arg	Gly	Ser	Pro	Arg	Ser	Glu	Arg	Ala	Arg	Arg	Ser	Ser
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Ser Arg Leu Arg Gln Arg Asp Pro Thr Ser Ala Ala Gly Leu Arg Arg
20 25 30

Glu	Ile	Arg	Pro	Gly	Leu	Pro	Glu	Ser	Glu	Pro	Arg	Pro	Pro	Arg	Pro
35															

Pro Ala Ala Leu Thr Ala Asp Gln Pro Pro Pro Arg Arg Leu Ser Glu
50 55 60

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Ser Arg Gly Gly Gly Met Ser Glu Ala Gly Glu Ala Thr Thr Thr
 65 70 75 80

Thr Thr Thr Leu Pro Gln Ala Pro Thr Glu Ala Ala Ala Ala Ala
 85 90 95

Pro Gln Asp Pro Ala Pro Lys Ser Pro Val Gly Ser Gly Ala Pro Gln
 100 105 110

Ala Ala Ala Pro Ala Pro Ala Ala His Val Ala Gly Asn Pro Gly Gly
 115 120 125

Asp Ala Ala Pro Ala Ala Thr Gly Thr Ala Ala Ala Ala Ser Leu Ala
 130 135 140

Ala Ala Ala Gly Ser Glu Asp Ala Glu Lys Lys Val Leu Ala Thr Lys
 145 150 155 160

Val Leu Gly Thr Val Lys Trp Phe Asn Val Arg Asn Gly Tyr Gly Phe
 165 170 175

Ile Asn Arg Asn Asp Thr Lys Glu Asp Val Phe Val His Gln Thr Ala
 180 185 190

Ile Lys Lys Asn Asn Pro Arg Lys Tyr Leu Arg Ser Val Gly Asp Gly
 195 200 205

Glu Thr Val Glu Phe Asp Val Val Glu Gly Glu Lys Gly Ala Glu Ala
 210 215 220

Ala Asn Val Thr Gly Pro Asp Gly Val Pro Val Glu Gly Ser Arg Tyr
 225 230 235 240

Ala Ala Asp Arg Arg Arg Tyr Arg Arg Gly Tyr Tyr Gly Arg Arg Arg
 245 250 255

Gly Pro Pro Arg Asn Tyr Ala Gly Glu Glu Glu Glu Gly Ser Gly
 260 265 270

Ser Ser Glu Gly Phe Asp Pro Pro Ala Thr Asp Arg Gln Phe Ser Gly
 275 280 285

Ala Arg Asn Gln Leu Arg Arg Pro Gln Tyr Arg Pro Gln Tyr Arg Gln
 290 295 300

Arg Arg Phe Pro Pro Tyr His Val Gly Gln Thr Phe Asp Arg Arg Ser
 305 310 315 320

Arg Val Leu Pro His Pro Asn Arg Ile Gln Ala Gly Glu Ile Gly Glu
 325 330 335

Met Lys Asp Gly Val Pro Glu Gly Ala Gln Leu Gln Gly Pro Val His
 340 345 350

Arg Asn Pro Thr Tyr Arg Pro Arg Tyr Arg Ser Arg Gly Pro Pro Arg
 355 360 365

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Pro Arg Pro Ala Pro Ala Val Gly Glu Ala Glu Asp Lys Glu Asn Gln
370 375 380

Gln Ala Thr Ser Gly Pro Asn Gln Pro Ser Val Arg Arg Gly Tyr Arg
385 390 395 400

Arg Pro Tyr Asn Tyr Arg Arg Pro Pro Ser Ser
405 410

<210> 125

<211> 2963

<212> DNA

<213> Homo sapiens

<400> 125

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cagatggagc tgcccaagaa agccttcattt accaacttct ccatgaacat cgatggcatg 300
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2400
2460
2520

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 cacgttggag ggacccttgg ccagtttac caggaggtgc tctgggatc tccagcagca 2700
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<210> 126
<211> 930
<212> PRT
<213> Homo sapiens

<400> 126
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 20 25 30
 Ile Asp Ile Tyr Ser Leu Thr Val Asp Ser Arg Val Ser Ser Arg Phe
 35 40 45
 Ala His Thr Val Val Thr Ser Arg Val Val Asn Arg Ala Asn Thr Val
 50 55 60
 Gln Glu Ala Thr Phe Gln Met Glu Leu Pro Lys Lys Ala Phe Ile Thr
 65 70 75 80
 Asn Phe Ser Met Asn Ile Asp Gly Met Thr Tyr Pro Gly Ile Ile Lys
 85 90 95
 Glu Lys Ala Glu Ala Gln Ala Gln Tyr Ser Ala Ala Val Ala Lys Gly
 100 105 110
 Lys Asn Ala Gly Leu Val Lys Ala Thr Gly Arg Asn Met Glu Gln Phe
 115 120 125
 Gln Val Ser Val Ser Val Ala Pro Asn Ala Lys Ile Thr Phe Glu Leu
 130 135 140
 Val Tyr Glu Glu Leu Leu Lys Arg Arg Leu Gly Val Tyr Glu Leu Leu
 145 150 155 160
 Leu Lys Val Arg Pro Gln Gln Leu Val Lys His Leu Gln Met Asp Ile
 165 170 175
 His Ile Phe Glu Pro Gln Gly Ile Ser Phe Leu Glu Thr Glu Ser Thr
 180 185 190
 Phe Met Thr Asn Gln Leu Val Asp Ala Leu Thr Thr Trp Gln Asn Lys
 195 200 205
 Thr Lys Ala His Ile Arg Phe Lys Pro Thr Leu Ser Gln Gln Gln Lys
 210 215 220

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Ser Pro Glu Gln Gln Glu Thr Val Leu Asp Gly Asn Leu Ile Ile Arg
 225 230 235 240

 Tyr Asp Val Asp Arg Ala Ile Ser Gly Gly Ser Ile Gln Ile Glu Asn
 245 250 255

 Gly Tyr Phe Val His Tyr Phe Ala Pro Glu Gly Leu Thr Thr Met Pro
 260 265 270

 Lys Asn Val Val Phe Val Ile Asp Lys Ser Gly Ser Met Ser Gly Arg
 275 280 285

 Lys Ile Gln Gln Thr Arg Glu Ala Leu Ile Lys Ile Leu Asp Asp Leu
 290 295 300

 Ser Pro Arg Asp Gln Phe Asn Leu Ile Val Phe Ser Thr Glu Ala Thr
 305 310 315 320

 Gln Trp Arg Pro Ser Leu Val Pro Ala Ser Ala Glu Asn Val Asn Lys
 325 330 335

 Ala Arg Ser Phe Ala Ala Gly Ile Gln Ala Leu Gly Gly Thr Asn Ile
 340 345 350

 Asn Asp Ala Met Leu Met Ala Val Gln Leu Leu Asp Ser Ser Asn Gln
 355 360 365

 Glu Glu Arg Leu Pro Glu Gly Ser Val Ser Leu Ile Ile Leu Leu Thr
 370 375 380

 Asp Gly Asp Pro Thr Val Gly Glu Thr Asn Pro Arg Ser Ile Gln Asn
 385 390 395 400

 Asn Val Arg Glu Ala Val Ser Gly Arg Tyr Ser Leu Phe Cys Leu Gly
 405 410 415

 Phe Gly Phe Asp Val Ser Tyr Ala Phe Leu Glu Lys Leu Ala Leu Asp
 420 425 430

 Asn Gly Gly Leu Ala Arg Arg Ile His Glu Asp Ser Asp Ser Ala Leu
 435 440 445

 Gln Leu Gln Asp Phe Tyr Gln Glu Val Ala Asn Pro Leu Leu Thr Ala
 450 455 460

 Val Thr Phe Glu Tyr Pro Ser Asn Ala Val Glu Glu Val Thr Gln Asn
 465 470 475 480

 Asn Phe Arg Leu Leu Phe Lys Gly Ser Glu Met Val Val Ala Gly Lys
 485 490 495

 Leu Gln Asp Arg Gly Pro Asp Val Leu Thr Ala Thr Val Ser Gly Lys
 500 505 510

 Leu Pro Thr Gln Asn Ile Thr Phe Gln Thr Glu Ser Ser Val Ala Glu
 515 520 525

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Gln Glu Ala Glu Phe Gln Ser Pro Lys Tyr Ile Phe His Asn Phe Met
 530 535 540
 Glu Arg Leu Trp Ala Tyr Leu Thr Ile Gln Gln Leu Leu Glu Gln Thr
 545 550 555 560
 Val Ser Ala Ser Asp Ala Asp Gln Gln Ala Leu Arg Asn Gln Ala Leu
 565 570 575
 Asn Leu Ser Leu Ala Tyr Ser Phe Val Thr Pro Leu Thr Ser Met Val
 580 585 590
 Val Thr Lys Pro Asp Asp Gln Glu Gln Ser Gln Val Ala Glu Lys Pro
 595 600 605
 Met Glu Gly Glu Ser Arg Asn Arg Asn Val His Ser Gly Ser Thr Phe
 610 615 620
 Phe Lys Tyr Tyr Leu Gln Gly Ala Lys Ile Pro Lys Pro Glu Ala Ser
 625 630 635 640
 Phe Ser Pro Arg Arg Gly Trp Asn Arg Gln Ala Gly Ala Ala Gly Ser
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 Arg Met Asn Phe Arg Pro Gly Val Leu Ser Ser Arg Gln Leu Gly Leu
 660 665 670
 Pro Gly Pro Pro Asp Val Pro Asp His Ala Ala Tyr His Pro Phe Arg
 675 680 685
 Arg Leu Ala Ile Leu Pro Ala Ser Ala Pro Pro Ala Thr Ser Asn Pro
 690 695 700
 Asp Pro Ala Val Ser Arg Val Met Asn Met Lys Ile Glu Glu Thr Thr
 705 710 715 720
 Met Thr Thr Gln Thr Pro Ala Pro Ile Gln Ala Pro Ser Ala Ile Leu
 725 730 735
 Pro Leu Pro Gly Gln Ser Val Glu Arg Leu Cys Val Asp Pro Arg His
 740 745 750
 Arg Gln Gly Pro Val Asn Leu Leu Ser Asp Pro Glu Gln Gly Val Glu
 755 760 765
 Val Thr Gly Gln Tyr Glu Arg Glu Lys Ala Gly Phe Ser Trp Ile Glu
 770 775 780
 Val Thr Phe Lys Asn Pro Leu Val Trp Val His Ala Ser Pro Glu His
 785 790 795 800
 Val Val Val Thr Arg Asn Arg Arg Ser Ser Ala Tyr Lys Trp Lys Glu
 805 810 815
 Thr Leu Phe Ser Val Met Pro Gly Leu Lys Met Thr Met Asp Lys Thr
 820 825 830

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Gly Leu Leu Leu Leu Ser Asp Pro Asp Lys Val Thr Ile Gly Leu Leu
 835 840 845

Phe Trp Asp Gly Arg Gly Glu Gly Leu Arg Leu Leu Leu Arg Asp Thr
 850 855 860

Asp Arg Phe Ser Ser His Val Gly Gly Thr Leu Gly Gln Phe Tyr Gln
 865 870 875 880

Glu Val Leu Trp Gly Ser Pro Ala Ala Ser Asp Asp Gly Arg Arg Thr
 885 890 895

Leu Arg Val Gln Gly Asn Asp His Ser Ala Thr Arg Glu Arg Arg Leu
 900 905 910

Asp Tyr Gln Glu Gly Pro Pro Gly Val Glu Ile Ser Cys Trp Ser Val
 915 920 925

Glu Leu
 930

<210> 127

<211> 191

<212> PRT

<213> Homo sapiens

<400> 127

Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu
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Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly
 20 25 30

Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln
 35 40 45

Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu
 50 55 60

Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu
 65 70 75 80

Met Arg Cys Gly Gly Cys Ser Asn Asp Glu Gly Leu Glu Cys Val Pro
 85 90 95

Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His
 100 105 110

Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys
 115 120 125

Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Asn Pro Cys Gly
 130 135 140

Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln Asp Pro Gln Thr
 145 150 155 160

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Cys Lys Cys Ser Cys Lys Asn Thr His Ser Arg Cys Lys Ala Arg Gln
165 170 175

Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys Pro Arg Arg
180 185 190

<210> 128

<211> 221

<212> PRT

<213> Homo sapiens

<400> 128

Met Pro Val Met Arg Leu Phe Pro Cys Phe Leu Gln Leu Leu Ala Gly
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Asn Gly Ser Ser Glu Val Glu Val Val Pro Phe Gln Glu Val Trp Gly
35 40 45

Arg Ser Tyr Cys Arg Ala Leu Glu Arg Leu Val Asp Val Val Ser Glu
50 55 60

Tyr Pro Ser Glu Val Glu His Met Phe Ser Pro Ser Cys Val Ser Leu
65 70 75 80

Leu Arg Cys Thr Gly Cys Cys Gly Asp Glu Asn Leu His Cys Val Pro
85 90 95

Val Glu Thr Ala Asn Val Thr Met Gln Leu Leu Lys Ile Arg Ser Gly
100 105 110

Asp Arg Pro Ser Tyr Val Glu Leu Thr Phe Ser Gln His Val Arg Cys
115 120 125

Glu Cys Arg His Ser Pro Gly Arg Gln Ser Pro Asp Met Pro Gly Asp
130 135 140

Phe Arg Ala Asp Ala Pro Ser Phe Leu Pro Pro Arg Arg Ser Leu Pro
145 150 155 160

Met Leu Phe Arg Met Glu Trp Gly Cys Ala Leu Thr Gly Ser Gln Ser
165 170 175

Ala Val Trp Pro Ser Ser Pro Val Pro Glu Glu Ile Pro Arg Met His
180 185 190

Pro Gly Arg Asn Gly Lys Lys Gln Gln Arg Lys Pro Leu Arg Glu Lys
195 200 205

Met Lys Pro Glu Arg Cys Gly Asp Ala Val Pro Arg Arg
210 215 220

<210> 129

<211> 1356

102/147

<212> PRT

<213> Homo sapiens

<400> 129

Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu
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Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro
20 25 30

Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
35 40 45

Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
50 55 60

Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser
65 70 75 80

Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn
85 90 95

Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser
100 105 110

Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser
115 120 125

Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys
130 135 140

Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser
145 150 155 160

Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn Arg
165 170 175

Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met Ile
180 185 190

Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu Ser
195 200 205

Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile Tyr
210 215 220

Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
225 230 235 240

Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
245 250 255

Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
260 265 270

Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
275 280 285

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Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
290 295 300

Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
305 310 315 320

Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met
325 330 335

Glu Ser Leu Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro Ala
340 345 350

Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly
355 360 365

Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr
370 375 380

Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu
385 390 395 400

Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val
405 410 415

Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro Val
420 425 430

Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val Tyr
435 440 445

Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu Glu
450 455 460

Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro Tyr
465 470 475 480

Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn Lys
485 490 495

Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn Lys
500 505 510

Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr
515 520 525

Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser
530 535 540

Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln
545 550 555 560

Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser
565 570 575

Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro
580 585 590

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Ile	His	Val	Gly	Glu	Leu	Pro	Thr	Pro	Val	Cys	Lys	Asn	Leu	Asp	Thr
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Leu	Trp	Lys	Leu	Asn	Ala	Thr	Met	Phe	Ser	Asn	Ser	Thr	Asn	Asp	Ile
610						615							620		
Leu	Ile	Met	Glu	Leu	Lys	Asn	Ala	Ser	Leu	Gln	Asp	Gln	Gly	Asp	Tyr
625					630					635					640
Val	Cys	Leu	Ala	Gln	Asp	Arg	Lys	Thr	Lys	Lys	Arg	His	Cys	Val	Val
					645				650					655	
Arg	Gln	Leu	Thr	Val	Leu	Glu	Arg	Val	Ala	Pro	Thr	Ile	Thr	Gly	Asn
				660				665					670		
Leu	Glu	Asn	Gln	Thr	Thr	Ser	Ile	Gly	Glu	Ser	Ile	Glu	Val	Ser	Cys
				675				680				685			
Thr	Ala	Ser	Gly	Asn	Pro	Pro	Pro	Gln	Ile	Met	Trp	Phe	Lys	Asp	Asn
				690				695			700				
Glu	Thr	Leu	Val	Glu	Asp	Ser	Gly	Ile	Val	Leu	Lys	Asp	Gly	Asn	Arg
				705				710			715			720	
Asn	Leu	Thr	Ile	Arg	Arg	Val	Arg	Lys	Glu	Asp	Glu	Gly	Leu	Tyr	Thr
				725				730					735		
Cys	Gln	Ala	Cys	Ser	Val	Leu	Gly	Cys	Ala	Lys	Val	Glu	Ala	Phe	Phe
				740				745				750			
Ile	Ile	Glu	Gly	Ala	Gln	Glu	Lys	Thr	Asn	Leu	Glu	Ile	Ile	Ile	Leu
				755				760				765			
Val	Gly	Thr	Ala	Val	Ile	Ala	Met	Phe	Phe	Trp	Leu	Leu	Leu	Val	Ile
				770				775			780				
Ile	Leu	Arg	Thr	Val	Lys	Arg	Ala	Asn	Gly	Gly	Glu	Leu	Lys	Thr	Gly
				785				790			795			800	
Tyr	Leu	Ser	Ile	Val	Met	Asp	Pro	Asp	Glu	Leu	Pro	Leu	Asp	Glu	His
				805				810				815			
Cys	Glu	Arg	Leu	Pro	Tyr	Asp	Ala	Ser	Lys	Trp	Glu	Phe	Pro	Arg	Asp
				820				825				830			
Arg	Leu	Lys	Leu	Gly	Lys	Pro	Leu	Gly	Arg	Gly	Ala	Phe	Gly	Gln	Val
				835				840				845			
Ile	Glu	Ala	Asp	Ala	Phe	Gly	Ile	Asp	Lys	Thr	Ala	Thr	Cys	Arg	Thr
				850				855			860				
Val	Ala	Val	Lys	Met	Leu	Lys	Glu	Gly	Ala	Thr	His	Ser	Glu	His	Arg
				865				870			875			880	
Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	His	His	Leu
				885				890				895			

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Asn Val Val Asn Leu Leu Gly Ala Cys Thr Lys Pro Gly Gly Pro Leu
 900 905 910

Met Val Ile Val Glu Phe Cys Lys Phe Gly Asn Leu Ser Thr Tyr Leu
 915 920 925

Arg Ser Lys Arg Asn Glu Phe Val Pro Tyr Lys Thr Lys Gly Ala Arg
 930 935 940

Phe Arg Gln Gly Lys Asp Tyr Val Gly Ala Ile Pro Val Asp Leu Lys
 945 950 955 960

Arg Arg Leu Asp Ser Ile Thr Ser Ser Gln Ser Ser Ala Ser Ser Gly
 965 970 975

Phe Val Glu Glu Lys Ser Leu Ser Asp Val Glu Glu Glu Ala Pro
 980 985 990

Glu Asp Leu Tyr Lys Asp Phe Leu Thr Leu Glu His Leu Ile Cys Tyr
 995 1000 1005

Ser Phe Gln Val Ala Lys Gly Met Glu Phe Leu Ala Ser Arg Lys Cys
 1010 1015 1020

Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Lys Asn
 1025 1030 1035 1040

Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp
 1045 1050 1055

Pro Asp Tyr Val Arg Lys Gly Asp Ala Arg Leu Pro Leu Lys Trp Met
 1060 1065 1070

Ala Pro Glu Thr Ile Phe Asp Arg Val Tyr Thr Ile Gln Ser Asp Val
 1075 1080 1085

Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Ala Ser
 1090 1095 1100

Pro Tyr Pro Gly Val Lys Ile Asp Glu Glu Phe Cys Arg Arg Leu Lys
 1105 1110 1115 1120

Glu Gly Thr Arg Met Arg Ala Pro Asp Tyr Thr Thr Pro Glu Met Tyr
 1125 1130 1135

Gln Thr Met Leu Asp Cys Trp His Gly Glu Pro Ser Gln Arg Pro Thr
 1140 1145 1150

Phe Ser Glu Leu Val Glu His Leu Gly Asn Leu Leu Gln Ala Asn Ala
 1155 1160 1165

Gln Gln Asp Gly Lys Asp Tyr Ile Val Leu Pro Ile Ser Glu Thr Leu
 1170 1175 1180

Ser Met Glu Glu Asp Ser Gly Leu Ser Leu Pro Thr Ser Pro Val Ser
 1185 1190 1195 1200

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Cys Met Glu Glu Glu Val Cys Asp Pro Lys Phe His Tyr Asp Asn
 1205 1210 1215

Thr Ala Gly Ile Ser Gln Tyr Leu Gln Asn Ser Lys Arg Lys Ser Arg
 1220 1225 1230

Pro Val Ser Val Lys Thr Phe Glu Asp Ile Pro Leu Glu Glu Pro Glu
 1235 1240 1245

Val Lys Val Ile Pro Asp Asp Asn Gln Thr Asp Ser Gly Met Val Leu
 1250 1255 1260

Ala Ser Glu Glu Leu Lys Thr Leu Glu Asp Arg Thr Lys Leu Ser Pro
 1265 1270 1275 1280

Ser Phe Gly Gly Met Val Pro Ser Lys Ser Arg Glu Ser Val Ala Ser
 1285 1290 1295

Glu Gly Ser Asn Gln Thr Ser Gly Tyr Gln Ser Gly Tyr His Ser Asp
 1300 1305 1310

Asp Thr Asp Thr Thr Val Tyr Ser Ser Glu Glu Ala Glu Leu Leu Lys
 1315 1320 1325

Leu Ile Glu Ile Gly Val Gln Thr Gly Ser Thr Ala Gln Ile Leu Gln
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Pro Asp Ser Gly Thr Thr Leu Ser Ser Pro Pro Val
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<210> 130

<211> 98

<212> PRT

<213> Homo sapiens

<400> 130

Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu
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Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys
 20 25 30

Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu
 35 40 45

Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala
 50 55 60

Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys
 65 70 75 80

Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser Lys Arg
 85 90 95

Ser Pro

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<210> 131

<211> 94

<212> PRT

<213> Homo sapiens

<400> 131

Met	Ser	Val	Lys	Gly	Met	Ala	Ile	Ala	Leu	Ala	Val	Ile	Leu	Cys	Ala
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Thr	Val	Val	Gln	Gly	Phe	Pro	Met	Phe	Lys	Arg	Gly	Arg	Cys	Leu	Cys
							20		25				30		

Ile	Gly	Pro	Gly	Val	Lys	Ala	Val	Lys	Val	Ala	Asp	Ile	Glu	Lys	Ala
						35			40			45			

Ser	Ile	Met	Tyr	Pro	Ser	Asn	Asn	Cys	Asp	Lys	Ile	Glu	Val	Ile	Ile
						50		55			60				

Thr	Leu	Lys	Glu	Asn	Lys	Gly	Gln	Arg	Cys	Leu	Asn	Pro	Lys	Ser	Lys
					65		70			75			80		

Gln	Ala	Arg	Leu	Ile	Ile	Lys	Lys	Val	Glu	Arg	Lys	Asn	Phe		
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<210> 132

<211> 5102

<212> DNA

<213> Homo sapiens

<400> 132

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aa 5102

<210> 133
<211> 1450
<212> DNA
<213> *Homo sapiens*

<400> 133
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<400> 141

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<211> 1137

<212> DNA

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<211> 1270

<212> DNA

<213> Homo sapiens

<400> 143

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<211> 3953

<212> DNA

<213> Homo sapiens

<400> 144

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 <213> Homo sapiens

<400> 156

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135/147

<212> DNA

<213> Homo sapiens

<400> 157

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<211> 155

<212> DNA

<213> Homo sapiens

<400> 158

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<211> 312

<212> DNA

<213> Homo sapiens

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136/147

<210> 160

<211> 447

<212> DNA

<213> Homo sapiens

<400> 160

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<210> 161

<211> 341

<212> DNA

<213> Homo sapiens

<400> 161

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<211> 288

<212> DNA

<213> Homo sapiens

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<210> 163

<211> 372

<212> DNA

<213> Homo sapiens

<400> 163

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137/147

<210> 164

<211> 483

<212> DNA

<213> Homo sapiens

<400> 164

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<210> 165

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<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

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25

<210> 166

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 166

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24

<210> 167

<211> 16

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Probe

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16

<210> 168

<211> 30

<212> DNA

<213> Artificial Sequence

138/147

<220>
<223> Description of Artificial Sequence: Primer

<400> 168
cctgatataa atgcaatatt aatgccttta 30

<210> 169
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 169
aagaaccggg agagcaaaca t 21

<210> 170
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 170
atctatgcc aagatcactt 20

<210> 171
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 171
ggagcacccgc ctgtgaa 17

<210> 172
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 172
tgtgcgttgc ctgaatgaac 20

<210> 173
<211> 16

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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 173
accaacctga agacac

16

<210> 174
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 174
tctcgactga atggactttg ca

22

<210> 175
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 175
tttgtgtaccc cgcaccaa

18

<210> 176
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 176
cacacctcta tcccgcc

17

<210> 177
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 177
gctgcatgtg gatcctgaga

20

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<210> 178
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 178
tgagtagcca gaataatcac catca

25

<210> 179
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Probe

<400> 179
cttcaagctc ctgggtaa

18

<210> 180
<211> 136
<212> DNA
<213> Homo sapiens

<400> 180
ggtgccgcaca gctgccgcac cagccccaaac accattgagg gagctgggag accctccca 60
cagtgcacc catgcagctg ctccccaggc caccccgctg atggagcccc accttgtctg 120
ctaaataaac atgtgc 136

<210> 181
<211> 1066
<212> PRT
<213> Homo sapiens

<400> 181
Met Pro Val Phe His Thr Arg Thr Ile Glu Ser Ile Leu Glu Pro Val
1 5 10 15

Ala Gln Gln Ile Ser His Leu Val Ile Met His Glu Glu Gly Glu Val
20 25 30

Asp Gly Lys Ala Ile Pro Asp Leu Thr Ala Pro Val Ala Ala Val Gln
35 40 45

Ala Ala Val Ser Asn Leu Val Arg Val Gly Lys Glu Thr Val Gln Thr
50 55 60

Thr Glu Asp Gln Ile Leu Lys Arg Asp Met Pro Pro Ala Phe Ile Lys
65 70 75 80

Val Glu Asn Ala Cys Thr Lys Leu Val Gln Ala Ala Gln Met Leu Gln
85 90 95

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Ser Asp Pro Tyr Ser Val Pro Ala Arg Asp Tyr Leu Ile Asp Gly Ser
100 105 110

Arg Gly Ile Leu Ser Gly Thr Ser Asp Leu Leu Leu Thr Phe Asp Glu
115 120 125

Ala Glu Val Arg Lys Ile Ile Arg Val Cys Lys Gly Ile Leu Glu Tyr
130 135 140

Leu Thr Val Ala Glu Val Val Glu Thr Met Glu Asp Leu Val Thr Tyr
145 150 155 160

Thr Lys Asn Leu Gly Pro Gly Met Thr Lys Met Ala Lys Met Ile Asp
165 170 175

Glu Arg Gln Gln Glu Leu Thr His Gln Glu His Arg Val Met Leu Val
180 185 190

Asn Ser Met Asn Thr Val Lys Glu Leu Leu Pro Val Leu Ile Ser Ala
195 200 205

Met Lys Ile Phe Val Thr Thr Lys Asn Ser Lys Asn Gln Gly Ile Glu
210 215 220

Glu Ala Leu Lys Asn Arg Asn Phe Thr Val Glu Lys Met Ser Ala Glu
225 230 235 240

Ile Asn Glu Ile Ile Arg Val Leu Gln Leu Thr Ser Trp Asp Glu Asp
245 250 255

Ala Trp Ala Ser Lys Asp Thr Glu Ala Met Lys Arg Ala Leu Ala Ser
260 265 270

Ile Asp Ser Lys Leu Asn Gln Ala Lys Gly Trp Leu Arg Asp Pro Ser
275 280 285

Ala Ser Pro Gly Asp Ala Gly Glu Gln Ala Ile Arg Gln Ile Leu Asp
290 295 300

Glu Ala Gly Lys Val Gly Glu Leu Cys Ala Gly Lys Glu Arg Arg Glu
305 310 315 320

Ile Leu Gly Thr Cys Lys Met Leu Gly Gln Met Thr Asp Gln Val Ala
325 330 335

Asp Leu Arg Ala Arg Gly Gln Gly Ser Ser Pro Val Ala Met Gln Lys
340 345 350

Ala Gln Gln Val Ser Gln Gly Leu Asp Val Leu Thr Ala Lys Val Glu
355 360 365

Asn Ala Ala Arg Lys Leu Glu Ala Met Thr Asn Ser Lys Gln Ser Ile
370 375 380

Ala Lys Lys Ile Asp Ala Ala Gln Asn Trp Leu Ala Asp Pro Asn Gly
385 390 395 400

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Gly Pro Glu Gly Glu Glu Gln Ile Arg Gly Ala Leu Ala Glu Ala Arg
405 410 415

Lys Ile Ala Glu Leu Cys Asp Asp Pro Lys Glu Arg Asp Asp Ile Leu
420 425 430

Arg Ser Leu Gly Glu Ile Ser Ala Leu Thr Ser Lys Leu Ala Asp Leu
435 440 445

Arg Arg Gln Gly Lys Gly Asp Ser Pro Glu Ala Arg Ala Leu Ala Lys
450 455 460

Gln Val Ala Thr Ala Leu Gln Asn Leu Gln Thr Lys Thr Asn Arg Ala
465 470 475 480

Val Ala Asn Ser Arg Pro Ala Lys Ala Ala Val His Leu Glu Gly Lys
485 490 495

Ile Glu Gln Ala Gln Arg Trp Ile Asp Asn Pro Thr Val Asp Asp Arg
500 505 510

Gly Val Gly Gln Ala Ala Ile Arg Gly Leu Val Ala Glu Gly His Arg
515 520 525

Leu Ala Asn Val Met Met Gly Pro Tyr Arg Gln Asp Leu Leu Ala Lys
530 535 540

Cys Asp Arg Val Asp Gln Leu Thr Ala Gln Leu Ala Asp Leu Ala Ala
545 550 555 560

Arg Gly Glu Gly Glu Ser Pro Gln Ala Arg Ala Leu Ala Ser Gln Leu
565 570 575

Gln Asp Ser Leu Lys Asp Leu Lys Ala Arg Met Gln Glu Ala Met Thr
580 585 590

Gln Glu Val Ser Asp Val Phe Ser Asp Thr Thr Thr Pro Ile Lys Leu
595 600 605

Leu Ala Val Ala Ala Thr Ala Pro Pro Asp Ala Pro Asn Arg Glu Glu
610 615 620

Val Phe Asp Glu Arg Ala Ala Asn Phe Glu Asn His Ser Gly Lys Leu
625 630 635 640

Gly Ala Thr Ala Glu Lys Ala Ala Ala Val Gly Thr Ala Asn Lys Ser
645 650 655

Thr Val Glu Gly Ile Gln Ala Ser Val Lys Thr Ala Arg Glu Leu Thr
660 665 670

Pro Gln Val Val Ser Ala Ala Arg Ile Leu Leu Arg Asn Pro Gly Asn
675 680 685

Gln Ala Ala Tyr Glu His Phe Glu Thr Met Lys Asn Gln Trp Ile Asp
690 695 700

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Asn Val Glu Lys Met Thr Gly Leu Val Asp Glu Ala Ile Asp Thr Lys
705 710 715 720

Ser Leu Leu Asp Ala Ser Glu Glu Ala Ile Lys Lys Asp Leu Asp Lys
725 730 735

Cys Lys Val Ala Met Ala Asn Ile Gln Pro Gln Met Leu Val Ala Gly
740 745 750

Ala Thr Ser Ile Ala Arg Arg Ala Asn Arg Ile Leu Leu Val Ala Lys
755 760 765

Arg Glu Val Glu Asn Ser Glu Asp Pro Lys Phe Arg Glu Ala Val Lys
770 775 780

Ala Ala Ser Asp Glu Leu Ser Lys Thr Ile Ser Pro Met Val Met Asp
785 790 795 800

Ala Lys Ala Val Ala Gly Asn Ile Ser Asp Pro Gly Leu Gln Lys Ser
805 810 815

Phe Leu Asp Ser Gly Tyr Arg Ile Leu Gly Ala Val Ala Lys Val Arg
820 825 830

Glu Ala Phe Gln Pro Gln Glu Pro Asp Phe Pro Pro Pro Pro Pro Asp
835 840 845

Leu Glu Gln Leu Arg Leu Thr Asp Glu Leu Ala Pro Pro Lys Pro Pro
850 855 860

Leu Pro Glu Gly Glu Val Pro Pro Pro Arg Pro Pro Pro Pro Glu Glu
865 870 875 880

Lys Asp Glu Glu Phe Pro Glu Gln Lys Ala Gly Glu Val Ile Asn Gln
885 890 895

Pro Met Met Met Ala Ala Arg Gln Leu His Asp Glu Ala Arg Lys Trp
900 905 910

Ser Ser Lys Gly Asn Asp Ile Ile Ala Ala Ala Lys Arg Met Ala Leu
915 920 925

Leu Met Ala Glu Met Ser Arg Leu Val Arg Gly Gly Ser Gly Thr Lys
930 935 940

Arg Ala Leu Ile Gln Cys Ala Lys Asp Ile Ala Lys Ala Ser Asp Glu
945 950 955 960

Val Thr Arg Leu Ala Lys Glu Val Ala Lys Gln Cys Thr Asp Lys Arg
965 970 975

Ile Arg Thr Asn Leu Leu Gln Val Cys Glu Arg Ile Pro Thr Ile Ser
980 985 990

Thr Gln Leu Lys Ile Leu Ser Thr Val Lys Ala Thr Met Leu Gly Arg
995 1000 1005

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Thr Asn Ile Ser Asp Glu Glu Ser Glu Gln Ala Thr Glu Met Leu Val
 1010 1015 1020

His Asn Ala Gln Asn Leu Met Gln Ser Val Lys Glu Thr Val Arg Glu
 1025 1030 1035 1040

Ala Glu Ala Ala Ser Ile Lys Ile Arg Thr Asp Ala Gly Phe Thr Leu
 1045 1050 1055

Arg Trp Val Arg Lys Thr Pro Trp Tyr Gln
 1060 1065

<210> 182

<211> 1666

<212> DNA

<213> Homo sapiens

<400> 182

ctccataagg cacaaaacttt cagagacacgc agagcacaca agcttcttagg acaagagcca 60
 ggaagaaaacc accggaaagga accatctcac tggctgtaaa catgacttcc aagctggccg 120
 tggctctctt ggcagccttc ctgatttctg cagctctgtg tgaaggtgca gttttgc当地 180
 ggagtgc当地 agaacttaga tgctc当地 gca taaagacata ctccaaacct ttccacccc当地 240
 aatttatcaa agaactgaga gtgattgaga gtggaccaca ctgc当地 cc当地 acagaaatta 300
 ttgttaaagct ttctgatgga agagagctct gtctggaccc caagggaaac tgggtgc当地 360
 gggttgtgga gaagttttt aagaggc当地 tggatcata aaaaaattca ttctctgtgg 420
 tatccaagaa tcagtgaaga tgccagtgaa acttcaagca aatctacttc aacacttcat 480
 gtattgtgtg ggtctgtgt agggttgcca gatgcaatac aagattc当地 tggatc当地 540
 aatttc当地 agttaaatttcat tgaccatga aatatccaga acataacttat 600
 atgttaaagta ttatttattt gaatctacaa aaaacaacaa ataattttta aatataagga 660
 ttttc当地 tattgc当地 cgg gagaatatac aaatagcaaa attgaggc当地 agggcc当地 720
 gaatatccgaa actttaattt caggaattga atgggttgc tagaatgtga tatttgaagc 780
 atcacataaaa aatgatggaa caataaattt tgccataaaag tcaaaattttag ctgaaatcc 840
 tggattttt tctgttaaat ctggcaaccc tagtctgcta gccaggatcc acaagtc当地 900
 gttccactgt gccttggttt ctcccttatt tctaagtggaa aaaagtatta gccaccatct 960
 tacctcacag tgatgtgtg aggacatgtg gaagcacttt aagtttttc atcataacat 1020
 aaatttattt caagtgtaac ttattaaacct atttatttatt tatgtattta tt当地 agcatc 1080
 aaatatattt gcaagaattt ggaaaaatag aagatgaatc attgattgaa tagttataaa 1140
 gatgttataat taaattttt ttattttttaga tattaaatga tgtttttatta gataaatttcc 1200
 aatcagggtt ttttagattaa acaaacaaaac aattgggtac ccagttaaat tttcatttca 1260
 gataaacaac aaataatttt ttagtataag tacattattt tttatctgaa attttattt 1320
 aactaacaat ccttagttga tactccc当地 ctgtcattt ccagctgtgt tggtagtgc当地 1380
 gtgttgaatt acgaaataat gagtttagaac tattaaacaa gccaaaactc cacagtcaat 1440
 attagtaatt tcttgctgtg tggaaacttgc ttattatgtt caaatagatt cttataat 1500
 tatttaaatg actgcatttt taaatacaag gctttatatt tt当地 aacttta agatgtttt 1560
 atgtgctctc caaattttt ttactgttcc tgattgtatg gaaatataaa agtaaataatg 1620
 aaacatttaa aatataattt gttgtcaaag taaaaaaaaaaaa aaaaaaa 1666

<210> 183

<211> 99

<212> PRT

<213> Homo sapiens

<400> 183

Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser
 1 5 10 15

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Ala	Ala	Leu	Cys	Glu	Gly	Ala	Val	Leu	Pro	Arg	Ser	Ala	Lys	Glu	Leu
20						25						30			

Arg	Cys	Gln	Cys	Ile	Lys	Thr	Tyr	Ser	Lys	Pro	Phe	His	Pro	Lys	Phe
35					40							45			

Ile	Lys	Glu	Leu	Arg	Val	Ile	Glu	Ser	Gly	Pro	His	Cys	Ala	Asn	Thr
50					55						60				

Glu	Ile	Ile	Val	Lys	Leu	Ser	Asp	Gly	Arg	Glu	Leu	Cys	Leu	Asp	Pro
65				70					75					80	

Lys	Glu	Asn	Trp	Val	Gln	Arg	Val	Val	Glu	Lys	Phe	Leu	Lys	Arg	Ala
85					90							95			

Glu Asn Ser

<210> 184

<211> 2480

<212> DNA

<213> Homo sapiens

<400> 184

tttgcttccc	ctcttccccga	agctctgaca	cctgccccaa	caagcaatgt	tggaaaat	ta	60
tttacatagt	ggcgcaaact	cccttactgc	tttggatata	aatccaggca	ggaggaggta		120
gctctaaggc	aagagatctg	ggacttctag	ccctctgaaact	ttcagccgaa	tacatcttt		180
ccaaaggagt	gaattcaggc	ccttgtatca	ctggcagcag	gacgtgacca	tggagaagct		240
gttgtgtttc	ttggcttga	ccagcctctc	tcatgctttt	ggccagacag	gtaaggggca		300
ccccaggct	tgggagagtt	ttgatctgag	gtatgggggt	ggggctcaag	actgcata	aa	360
cagtctcaa	aaaaaaaaaa	aaagactgta	tgaacagaac	agtggagcat	cottcatgtt		420
gttgtgtgt	gttgtgtgt	gttgtgtgg	tgtgtactg	gagaagggt	cagtctgtt		480
ctcaatctta	aattctatac	gtaagtgagg	ggatagatct	gtgtgatctg	agaaacctct		540
cacatttgc	tgttttctg	gctcacagac	atgtcgagga	aggctttgt	gtttccaaa		600
gagtcggata	cttcctatgt	atccctcaaa	gcaccgttaa	cgaagctct	caaagcctc		660
actgtgtgcc	tccacttcta	cacggactg	tcctcgaccc	gtgggtacag	tat	ttctcg	720
tatgccacca	agagacaaga	caatgagatt	ctcatat	ttt	ggtctaagga	tataggatac	780
agttttacag	tgggtgggc	tgaaatatta	ttcgaggtt	ctgaagt	tcac	atgtagctca	840
gtacacattt	gtacaagctg	ggagtcggcc	tcagggatcg	tggagttctg	gttagatgg		900
aagcccaggg	tgaggaagag	tctgaagaag	ggatacactg	tggggcaga	agcaagcatc		960
atcttggggc	aggagcagga	ttccttcgg	gggaactttt	aaggaa	gcca	gtccctgg	1020
ggagacat	gaaatgtgaa	catgtgggac	tttgcgtgt	caccagat	gat	taaacacc	1080
atctatctt	gcggccctt	cagtccaa	gtcctgaa	ggcggcact	gaagtatgaa		1140
gtgcaaggcg	aagtgttac	caaacc	ctgtggccct	gaggccag	gtgggtcc		1200
aaggtac	ccggttttt	acaccgc	ggcccacgt	ctctgtct	gtac	ctccc	1260
gctttttac	actgcattt	tcccacgt	ctgtctctt	gccttgc	ccctat	atgc	1320
attgaggct	gctccacc	cctcagc	tgagaatgg	gttaa	agtgt	ctggctt	1380
agctcg	tta	aaatgg	aaagaa	atc	atc	gtt	1440
cattttatt	tcaagttg	agatctt	agataattt	ttac	tcaca	tagatg	1500
aactaacacc	cagaaaggag	aaatgat	ataaaaaact	cata	aggca	gagctg	1560
ggaagcgt	atcttctatt	taattccca	cccatgaccc	ccagaa	agca	ggagcatt	1620
ccacattc	agg	ctt	tcaggac	ggcc	agggt	ctgg	1680
tccagagt	tcatcat	gtcata	tgctggccc	agg	tct	aaatgg	1740
cccagca	ccacgc	cctcc	ctcaa	act	gaaa	ccatt	1800
tgccccagca	gagcagat	gtt	cag	gaaa	tga	acta	1860
tgttgttact	gcca	act	taat	gact	gtt	gtt	1920

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tttatggctc ttctggaaa ctcctcccct tttccacacg aaccttgtgg ggctgtgaat 1980
tctttcttca tccccgcatt cccaataatac ccaggccaca agagtggacg tgaaccacag 2040
gtgtgtcctgt cagaggagcc catctccat ctccccagct ccctatctgg aggatagttg 2100
gatagttacg tgttccttagc aggaccaact acagtcttcc caaggattga gttatggact 2160
ttgggagtga gacatcttct tgctgctgga tttccaagct gagaggacgt gaacctggga 2220
ccaccagtag ccatcttggt tgccacatgg agagagactg tgaggacaga agccaaactg 2280
gaagtggagg agccaaggga ttgacaaaca acagagcctt gaccacgtgg agtctctgaa 2340
tcagccttgt ctggaaccag atctacacacct ggactgccca ggtctataag ccaataaaagc 2400
ccctgtttac ttgagtgagt ccaagctgtt ttctgatagt tgcttagaa gttgtgacta 2460
acttctctat gacctttgaa 2480

<210> 185

<211> 224

<212> PRT

<213> Homo sapiens

<400> 185

Met Glu Lys Leu Leu Cys Phe Leu Val Leu Thr Ser Leu Ser His Ala
1 5 10 15

Phe Gly Gln Thr Asp Met Ser Arg Lys Ala Phe Val Phe Pro Lys Glu
20 25 30

Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys Pro Leu
35 40 45

Lys Ala Phe Thr Val Cys Leu His Phe Tyr Thr Glu Leu Ser Ser Thr
50 55 60

Arg Gly Tyr Ser Ile Phe Ser Tyr Ala Thr Lys Arg Gln Asp Asn Glu
65 70 75 80

Ile Leu Ile Phe Trp Ser Lys Asp Ile Gly Tyr Ser Phe Thr Val Gly
85 90 95

Gly Ser Glu Ile Leu Phe Glu Val Pro Glu Val Thr Val Ala Pro Val
100 105 110

His Ile Cys Thr Ser Trp Glu Ser Ala Ser Gly Ile Val Glu Phe Trp
115 120 125

Val Asp Gly Lys Pro Arg Val Arg Lys Ser Leu Lys Lys Gly Tyr Thr
130 135 140

Val Gly Ala Glu Ala Ser Ile Ile Leu Gly Gln Glu Gln Asp Ser Phe
145 150 155 160

Gly Gly Asn Phe Glu Gly Ser Gln Ser Leu Val Gly Asp Ile Gly Asn
165 170 175

Val Asn Met Trp Asp Phe Val Leu Ser Pro Asp Glu Ile Asn Thr Ile
180 185 190

Tyr Leu Gly Gly Pro Phe Ser Pro Asn Val Leu Asn Trp Arg Ala Leu
195 200 205

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Lys Tyr Glu Val Gln Gly Glu Val Phe Thr Lys Pro Gln Leu Trp Pro
210 215 220